PROTOCOL VIS-2014

A PROSPECTIVE, MULTICENTER CLINICAL TRIAL OF
THE VISABILTY IMPLANT SYSTEM
FOR IMPROVEMENT OF NEAR VISUAL ACUITY IN PRESBYOPIC PATIENTS

Refocus Group, Inc.
10300 North Central Expressway
Suite 104
Dallas, TX 75231

Date of Protocol: October 13, 2014
Date of Protocol Amendment 2: March 3, 2015

I have read and agree to follow the study procedures as outlined in this protocol.

__________________________________________
Print Name of Investigator

__________________________________________
Investigators’ Signature Date

CONFIDENTIAL – DO NOT COPY OR DISTRIBUTE

This protocol contains confidential proprietary information with respect to Refocus products and clinical trials. I agree to hold this information in confidence and not to disclose it to any third parties for a period of three years from the date of this agreement, or until this information becomes a matter of public knowledge or until a formal agreement for that purpose has been entered into by the parties.
# TABLE OF CONTENTS

1.0 PERSONNEL AND FACILITIES ................................................................. 1

2.0 ABBREVIATIONS ..................................................................................... 2

3.0 STUDY SYNOPSIS .................................................................................... 4

4.0 BACKGROUND AND REGULATORY CHRONOLOGY ......................... 5

5.0 SCIENTIFIC BACKGROUND ON PRESBYOPIA ............................... 7

6.0 PRIOR SCLERAL IMPLANT CLINICAL STUDIES ............................. 10

7.0 STUDY OUTLINE .................................................................................. 13

8.0 STUDY METHODS ................................................................................. 16

10.0 ADVERSE EVENT REPORTING ............................................................. 30

11.0 STATISTICAL METHODS .................................................................. 35

12.0 MONITORING .................................................................................... 44

13.0 REFERENCES ....................................................................................... 45

**LIST OF APPENDICES**

Appendix 1 Examination Methods ............................................................. 46

Appendix 5 Data Safety Monitoring Board Charter .................................. 75

Appendix 6 Anterior Segment Ischemia; Detection, Mitigation and Reporting ................................................................. 81

Appendix 7 Sponsor Commitments ............................................................ 88

Appendix 8 Investigator Commitments and Responsibilities .................. 89

Appendix 9 Declaration of Helsinki ............................................................ 91
### 1.0 PERSONNEL AND FACILITIES

| **STUDY SPONSOR** | Refocus Group, Inc.  
10300 North Central Expressway  
Suite 104  
Dallas, TX 75231  
(214) 368-0200 |
|-------------------|---------------------------------------------------|
| **MEDICAL MONITOR** | Mark Packer, M.D.  
4075 Southpointe Drive  
Eugene, Oregon 97405  
(541) 915-0291 |
| **CLINICAL MONITOR** | Quality Data Services, Inc.  
1000 Continental Drive  
Suite 200  
King of Prussia, Pennsylvania 19406  
(610) 354-0404 |
2.0 ABBREVIATIONS

AE Adverse Event
AIDS Acquired Immune Deficiency Syndrome
ASI Anterior Segment Ischemia
BCDVA Best Corrected Distance Visual Acuity
BCNVA Best Corrected Near Visual Acuity
BSS Balanced Salt Solution
CPS Critical Print Size
CRF Case Report Form
CRO Clinical Research Organization
CRSE Cycloplegic Refraction Spherical Equivalent
CSLO Confocal Scanning Laser Ophthalmology
dB Decibel
DCNVA Distance Corrected Near Visual Acuity
eCRF electronic Case Report Form
EDC Electronic Data Capture
GCP Good Clinical Practice
HIV Human Immunodeficiency Virus
ICC Intraclass Correlation Coefficient
ICD International Classification of Diseases
ICF Informed Consent Form
IDE Investigational Device Exemption
IOL Intraocular Lens
IOP Intraocular Pressure
IRB Institutional Review Board
LASIK Laser Assisted In-Situ Keratomileusis
LogMAR Logarithm of the Minimum Angle of Resolution
LST Lamellar Scleral Tunnel
MD Mean Deviation
mm millimeters
mm Hg Millimeters of Mercury
MRSE Manifest Refraction Spherical Equivalent
NAVQ Near Acuity Visual Questionnaire
NSAID Non-Steroidal Anti-Inflammatory Drug
OCT Optical Coherence Tomography
OD Right Eye
OS Left Eye
PG Prostaglandin
PI Principal Investigator
PMA Premarket Approval
PMMA Polymethylmethacrylate
PRO Patient Reported Outcomes
PSD Pattern Standard Deviation
PSI PresVIEW Scleral Implants
PTFE Polytetrafluoroethylene
SAE Serious Adverse Event
SITA Swedish Interactive Threshold Algorithm
SOP Standard Operating Procedure
SPK Superficial Punctuate Keratitis
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>UADE</td>
<td>Unanticipated Adverse Device Effect</td>
</tr>
<tr>
<td>UBM</td>
<td>Ultrasound Biomicroscopy</td>
</tr>
<tr>
<td>UCDVA</td>
<td>Uncorrected Distance Visual Acuity</td>
</tr>
<tr>
<td>UCIVA</td>
<td>Uncorrected Intermediate Visual Acuity</td>
</tr>
<tr>
<td>UCNVA</td>
<td>Uncorrected Near Visual Acuity</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>VIS</td>
<td>VisAbility Implant</td>
</tr>
<tr>
<td>VIS</td>
<td>VisAbility Implant System</td>
</tr>
<tr>
<td>VR-QOL</td>
<td>Vision Related Quality of Life</td>
</tr>
</tbody>
</table>
3.0 STUDY SYNOPSIS

The objective of this study is to evaluate the safety and effectiveness of the VisAbility Implant System (VIS) for the improvement of near visual acuity in presbyopic patients. This is a prospective clinical study that will enroll and determine eligible a total of 360 subjects ranging in age between 45 and 60 years of age at up to 14 clinical sites. Subjects will be implanted with the VisAbility Implant [redacted] in the primary eye and then in the fellow eye no sooner than 14 days later. Subjects will be examined at one day, one week and at 1, 2, 3, 6, 12, 18 and 24 months post-operatively.

The study will also include a 60 subject randomized controlled sub-study at 3 investigational sites. Subjects enrolled and eligible at these sites will be randomized (1:1 ratio) to a surgery group or a control group. Subjects randomized to the surgery group will undergo surgery and will be followed for 24 months in the same manner as the larger non-randomized surgical group. Subjects randomized to the control group will be followed for 6 months, and will be eligible to undergo surgery after completion of this 6-month follow-up period.

The primary endpoint is achievement of distance corrected near visual acuity (DCNVA) of Snellen equivalent 20/40 or better (at 40 cm) and at least 10 letters (ETDRS) improvement in DCNVA in the primary eye.

This endpoint will be evaluated against two objectives, a) 75% or more of primary eyes achieve the effectiveness endpoint at 12 months postoperative and b) the percentage of primary eyes achieving the effectiveness endpoint at 6 months postoperative (6-month responder rate) is higher than the percentage in the randomized control group.

A PMA application will be submitted when the full study cohort has completed the 12 month follow-up visit.
4.0 BACKGROUND AND REGUALORY CHRONOLOGY

4.1 Background

Clinical evaluation of PresVIEW Scleral Implants (PSI) was initiated in 1997 following FDA approval of G970152. The initial clinical trial was a feasibility study in presbyopic subjects desiring improvement in near visual acuity. Based on the encouraging outcomes of the feasibility study a large clinical trial of the PSI was initiated in 2003 under Protocol P-277-5, and two models of the PSI have been evaluated.

The PSI model PSI-001 was implanted in 164 subjects (213 eyes) from 1999 through 2007. The PSI model SGP-046 was introduced in 2009 to provide better fixation of the PSI in the scleral tunnel. Since there were significant differences in the design of the PSI model PSI-001 and SGP-046, a full cohort of 330 subjects (645 eyes) was implanted.

Both scleral implant models PSI-001 and SGP-046 consist of four segments which are implanted in scleral tunnels in the four oblique quadrants of the eye. From 1999 through 2000, scleral tunnels were created using a diamond blade. An automated, electrically powered, re-usable device designed specifically for scleral tunnel creation, called the Scleratome, was introduced in 2003 and this incision system was used through mid-2012. In April 2012, FDA approved introduction of a smaller, lighter, disposable Scleratome into the ongoing IDE clinical trial. Since the tunnel configuration was the same for both Scleratomes, as demonstrated in performance testing submitted in the IDE supplement supporting introduction of the disposable Scleratome, Refocus assumed that clinical data from both the re-usable and the disposable Scleratome were expected to be comparable.

After introduction of the disposable Scleratome in May 2012, 56 subjects (119 eyes) were implanted in incisions made with this improved Scleratome. An exploratory analysis of 12 month clinical outcomes of these eyes as compared to eyes implanted with the earlier reusable Scleratome provided evidence of greater improvements in near vision with the disposable Scleratome. While this finding was unanticipated, it was also very encouraging since these improvements in near vision were achieved considerably earlier in the postoperative period.

This finding was also important since it confirmed Refocus’ expectation that improved surgical instrumentation would have a favorable effect on postoperative clinical outcomes, as evidenced in the transition from the original IDE pilot study in which scleral tunnels were created using a diamond blade to use of the automated, re-usable Scleratome introduced in 2003 and to the more recent introduction of the disposable Scleratome.

In Protocol P-277-5, conducted under G970152, the location of the scleral incisions for placement of the PSI was identified by marking the targeted position of the incisions. This method was not completely reliable since the marking can be difficult for the surgeon to see during the procedure. As a result, some surgeons had experienced difficulty placing the Scleratome in the proper position relative to the marks created.
4.2 Rationale for Protocol VIS-2014

In a further effort to develop improved surgical instrumentation that would provide more reliable placement of the scleral tunnels created by the Scleratome, the company has developed an integrated surgical instrumentation system, called the VisAbility Implant System.

The VisAbility Implant System consists of:

• VisAbility Implant (previously referred to as the PSI model SGP-046),
• VIS Docking Station (previously referred to as the Oculock)
• VIS Scleratome (the Docking and Scleratome together, previously called the "Oculock Incision System")
• Other custom surgical instruments for use during the procedure.

The Docking Station is a fixation device that addresses sources of variability in the creation of scleral tunnels and provides a simple method for placing the Scleratome in the correct location on the eye. The Docking Station provides stabilization of the eye and serves to "dock" the Scleratome during creation of the scleral tunnels, ensuring consistent placement of the 4 scleral tunnels to be created. Use of the Docking Station with the Scleratome is expected to result in a shorter duration procedure as well as in improved reproducibility of the implantation procedure.

The VisAbility Implant System, and specifically the Docking Station, prevents creation of scleral tunnels too close to the limbus by establishing a guide for the positioning of the Scleratome blade at a distance of approximately 4.0 millimeters from the corneal limbus. When the Docking Station is properly aligned, the 4 PSI segments will be equally spaced between the rectus muscles, minimizing the likelihood of pressure on the anterior ciliary muscles, which could result in reduced iris perfusion.

It should be noted that the PSI model SGP-046, renamed the VisAbility Implant, has not been modified since its introduction into the clinical trial conducted under G970152, and there are no plans to modify this implant.

Given the potential for the VisAbility Implant System to improve results of the implantation procedure, Protocol VIS-2014, a new pivotal trial, is being conducted to definitively evaluate the safety and effectiveness of the VisAbility Implant System.
5.0 SCIENTIFIC BACKGROUND ON PRESBYOPIA

Presbyopia is the most prevalent of all visual deficiencies, affecting virtually 100% of the population over the course of a normal life span. It is characterized by a progressive, age-related loss of accommodation, or the ability of the human eye to focus clearly on objects over a range of near to intermediate distances from the eye. By the fifth decade of life, the amplitude of accommodation has declined so that the near point of the eye is more remote than typical reading distance. Once presbyopia occurs, emmetropes will need an optical aid for near vision. Myopes will find they see better at near without their distance correction and hyperopes will require a correction for both distance and near vision.

When the eye accommodates to focus on a near object, convergence and pupil constriction also occur. The combination of these three movements (accommodation, convergence and miosis) is under the control of the Edinger-Westphal nucleus and is referred to as the near triad, or accommodation reflex. Accommodation is accomplished by the ability of the human eye to alter the refraction of the crystalline lens, depending on the distance of the object from the eye. In the eye of a presbyopic emmetrope, the lens cannot accommodate sufficiently to focus the light rays from a near object onto a single point on the retina. Thus, a point object is imaged as a blur circle on the retina. Loss of accommodation typically begins in mid-life, eventually culminating in a nearly complete loss of the ability of the eye to clearly visualize near objects.

Currently, no universally accepted surgical treatments are available for presbyopia. Vision correction options include near vision reading glasses and/or contact lenses. As the physiological mechanisms of accommodation are investigated, more therapeutic and corrective options are being explored. These include the use of multifocal intraocular lenses (IOLs), monovision and anisometropic corneal refractive surgical procedures using laser-assisted in situ keratomileusis (LASIK), corneal implant devices, and the VisAbility Implant.

5.1 Lenticular and Extralenticular Theories

The underlying cause(s) of presbyopia, loss of accommodation of the eye over time, is not completely understood or agreed upon by the medical community. Scientific theories for accommodative loss may be generally ascribed to two schools of thought:

- **Lenticular Theories** are broadly based on age-related changes in properties of the lens of the eye, including the lens substance, the lens capsule, and the zonular fibers. These theories stem not only from purported changes in the elasticity of the tissues, but also from continued growth and changes in the thickness and the curvature of the lens with age. Helmholtz’s lenticular theory of the loss of accommodation is the most widely accepted of these types of theories.¹ The majority of current approaches for the treatment of presbyopia are based upon lenticular theories of accommodation.

- **Extralenticular Theories** consider age-related changes in the accommodative structures outside of the lens, capsule, and zonules. These factors include anatomical, morphological, and physiological changes in the ciliary muscle, connective tissue, and choroid. The Scleral Implant approach to the treatment of presbyopia is based on extralenticular theories.
5.2 Theories of Accommodation

For the past 150 years, Helmholtz's lenticular theory of the loss of accommodation has been the accepted basis for the underlying physiological mechanisms that lead to presbyopia\(^1\) Helmholtz hypothesized that presbyopia is caused by the hardening of the lens with age. According to Helmholtz, as the ciliary body contracts for accommodation, it constricts inwardly and relaxes the zonules. The relaxation of the zonules causes the lens to "round up", and as the lens becomes more convex, it adds dioptric power thus bringing near objects into focus. According to Helmholtz’s theory, the decrease in flexibility of the lens and the loss in elasticity of the lens capsule that occur with aging progressively hinder the focusing mechanism.

Although generally accepted, Helmholtz's theory cannot fully explain the mechanism by which the lens alters its shape, nor can it satisfactorily explain the reason or means by which aging uniformly affects accommodation across the population.

An extralenticular theory that may explain age-related changes in accommodation is Dr. Jackson Coleman's catenary theory of accommodation.\(^2,3,4\) Coleman’s theory proposes that the lens, zonules, and anterior vitreous comprise a diaphragm between the anterior and vitreous chambers of the eye. According to Coleman, this construct behaves in a manner analogous to a hydraulic suspension bridge, or catenary. When the ciliary muscles contract to accommodate the lens, pressure is increased in the vitreous compartment.

Simultaneously, pressure in the anterior chamber is decreased due to the expansion of the trabecular meshwork, which occurs with ciliary body contraction. A pressure gradient is thus established between the 2 chambers, resulting in a posterior flattening of the lens and, anteriorly, in a steeper radius of curvature in the center of the lens with a slight flattening at the periphery.\(^6\)

The anterior capsule and the zonules form a hammock-shaped surface (a modified catenary) that can be predicted mathematically based on the circumference of the ciliary body (Müeller’s muscle).\(^7\) Much like the pylons of a suspension bridge, the ciliary body dictates the shape of the catenary. Thus, the accommodated state appears to be supported by the fluid volume differential with very little energy expenditure, much like a viscose-damped hydraulic door closer.

Coleman’s hypothesis has been tested by comparing a mechanical model of accommodation with in vivo measurements of lens geometry changes during accommodation (measurements included ultrasound, MRI, and optical techniques).\(^6,7,8\) The mechanical model consisted of fluid-filled latex balloons which were supported by a plastic wrap hammock to form a curve that potentially models the human lens. Increasing balloon volumes were used to simulate growth of the aging lens, and variations in curvature were measured.
Schachar proposed an alternative extralenticular theory. He hypothesized that presbyopia is a result of a decrease in distance between the ciliary muscles and lens equator. It is known that lens tissue continues to grow over the lifetime of an individual, while sclera stops growing at approximately age 13. Therefore, there is a linear decrease in the distance between the ciliary muscles and the lens over time. Ciliary muscles are smooth with striations, and thus, the amount of tension they can develop is directly related to the degree to which they are stretched. Over time, the amplitude of accommodation is reduced because the distance between the lens and the muscles is decreased, resulting in presbyopia. Stretching the ciliary muscles by surgical intervention would increase their ability to exert force on the lens and improve near vision.

More recently, Goldberg and colleagues have made efforts to incorporate the research findings of others in a computer-animated model of accommodation. Dr. Goldberg notes that, "A team of European investigators (Elke Lutjen-Drecoll, MD, and colleagues at the Institute of Anatomy in Erlangen, Germany) and American investigators (Mary Ann Croft, MS; Paul Kaufman, MD; and colleagues at the National Primate Lab and University of Wisconsin in Madison) have used electron microscopy and video ultrasound biomicroscopy (UBM) and endoscopy to define the complex, separate elements of the zonules and document the interconnected movements of the extralenticular tissues." Dr. Goldberg suggests that the mechanism of accommodation should include a new theory of reciprocal zonular action, which he describes as follows: "During ciliary body contraction, the anterior zonules lose tension while the posterior zonules stretch. During ciliary body relaxation, the posterior zonules lose tension as the lens flattens and is pulled back by the increasing tension of the anterior zonules."

The exact cause of the loss of accommodation over time is not known and may be associated with the above theories, a combination of these theories, or theories not yet introduced.
6.0 PRIOR SCLERAL IMPLANT CLINICAL STUDIES

As briefly described in the introduction to this protocol, Refocus has conducted a feasibility study of the scleral implants in 29 presbyopic subjects, followed by a pivotal trial that enrolled 135 subjects with the design of the PresVIEW Scleral Implant and 330 subjects. The results of these studies are described briefly below.

6.1 Feasibility Clinical Study

Clinical evaluation of the scleral implants was initiated in March 1999 following FDA approval of G970152. The feasibility clinical trial enrolled 29 presbyopic subjects desiring improvement in near visual acuity at 6 clinical sites. Subjects were implanted in the primary eye only and followed for 24 months. Four PMMA segments were implanted in partial thickness scleral tunnels in the four oblique quadrants of the eye. The scleral tunnels were made using a diamond blade.

While some study subjects experienced a clinically significant improvement in near visual acuity in this study, the effectiveness results were mixed as a result of difficulty in accurately and consistently creating the scleral tunnels. Notwithstanding these challenges, the initial results provided evidence of safety and effectiveness and supported initiation of a larger clinical trial. Importantly, the findings regarding difficulty in scleral tunnel creation led to development of an automated, electrically powered, re-usable incision device, the Scleratome, which was used in subsequent clinical studies.

6.2 Pivotal Trial of the Scleral Implant (Protocol P-277-5)

A prospective, randomized controlled multicenter clinical trial of the scleral implant was approved by FDA in December 2003. Subjects were implanted with the design and followed for 24 months. In the initial randomized controlled stage of this study, 150 subjects were to be randomized in a 2:1 ratio either to a surgical cohort (N=100) or to a Deferred Treatment / Control cohort (N=50) with an interim report to be provided to FDA upon obtained preliminary data on 75 randomized subjects. Subjects randomized to the deferred surgery/control cohort were eligible to receive the implant after completion of 6 months of follow-up in the study.

In the initial stage of this study, a total of 81 subjects were enrolled and randomized to either the PSI Treatment Group (53) or the Deferred Treatment Control Group (28) at a ratio of 2:1 per the study protocol. At the 3-month visit, 64% (23/36) of the eyes assigned to the PSI Treatment Group had distance corrected near visual acuity 20/40 or better, as compared with 6% (1/18) of Deferred Treatment Control Group. At the 6-month postoperative exam 70% (30/43) of the eyes in the PSI Treatment Group eyes had distance corrected near visual acuity 20/40 or better, as compared with 4% (1/23) of the Deferred Treatment Control eyes.

While these data supported expansion to the full study cohort of 330 subjects and up to 660 eyes, with bilateral implantation, only a total of 184 eyes of 135 subjects were implanted with the under this protocol.
Initial effectiveness outcomes were consistent with the results of the initial subjects in the randomized substudy, however the improvement in near visual acuity was not sustained over time in some subjects. During investigation of this unexpected finding, imaging of the PSI segments using the Visante OCT (Carl Zeiss Meditec, Jena, Germany) revealed displacement of at least one of the implant segments in subjects who experienced an initial improvement in near vision followed by loss of this improvement.

Subsequently, in a group of patients with displaced segments, repositioning and suturing of the segments was associated with clear improvements in near acuity, and confirmed that the stability of the PSI segments in the scleral tunnel was directly related to clinical efficacy.

Since suturing of the PSI significantly increased procedure time and complexity, Refocus deferred further enrollment in the study pending design changes to the scleral implant segment to resolve the displacement issue. A new design was developed, which incorporated a two part implant segment; a main body with “feet” at both ends that protruded beyond the edges of the tunnel and a secondary locking insert. This design, known as the PSI SGP-046, was introduced into Protocol P-277-5, and has been shown to reliably maintain the implant segment firmly in place, as described further below.

6.3 Pivotal Trial of the Scleral Implant (continuation of Protocol P-277-5)

The PSI Scleral Implant, designed to provide better fixation of the PSI in the scleral tunnel, was introduced into Protocol P-277-5 in June 2009. Since 135 subjects had already been enrolled and implanted with the PSI design, enrollment was increased to 465 subjects to ensure that 330 subjects could be enrolled and implanted with the PSI SGP-046 in support of a Premarket Approval Application (PMA).

With the modified design of the PSI segment, another 48 patients were to be enrolled in a sub-study and randomized (2:1 ratio) with 32 patients receiving the PSI and 16 deferred surgery/control patients. As before, subjects randomized to the deferred surgery/control cohort were eligible to receive the PSI after completion of 6 months of follow-up in the study. The results of patients who elected to have PSI surgery after completion of 6 months of follow-up in the deferred/control surgery group were included in the total patient cohort.

A smaller, lighter, disposable Scleratome was also introduced into the ongoing IDE clinical trial in April 2012. Since the tunnel configuration was the same for both Scleratomes, as demonstrated in performance testing, Refocus assumed that clinical data from both the re-usable and the disposable Scleratome would be comparable. However, an exploratory analysis of 12 month clinical outcomes for 56 primary eyes (119 total eyes) implanted with PSI using the disposable Scleratome showed greater improvements in near vision following surgery with this improved surgical tool as compared to earlier subjects in the cohort. While this finding was unanticipated, it was also very encouraging since the improvements in near vision were also achieved considerably earlier in the postoperative follow-up period. These findings were important since they confirmed Refocus’ expectation that improved surgical instrumentation would have a favorable impact on the post-operative clinical outcomes, as evidenced in the transition from the original IDE pilot study in which scleral tunnels were created using a diamond blade to use of the automated, re-usable Scleratome introduced in 2003 and to this more recent introduction of the disposable Scleratome.
A total of 645 eyes of 330 subjects were enrolled and implanted with the PSI [redacted] in this clinical study. Subjects implanted with the PSI [redacted] experienced clinically meaningful improvement with DCNVA (Sloan) at 40cm. DCNVA (Sloan) of 20/40 or better was achieved by 80% (237/298) of subjects at 12 months, by 84% (210/249) of subjects at 18 months and by 91% (120/132) of subjects at 24 months.

Further, during the course of this clinical trial no persistent loss in BCDVA or BCNVA was observed in any eye. BCDVA remained generally unchanged from baseline through the 24 month visit and all (100%) of the PSI treated eyes achieved BCNVA of 20/32 or better at all postoperative examinations.

The PSI [redacted] has not been modified since its introduction into the clinical trial conducted under G970152, and there are no plans to modify this model of the PSI.

Frequently reported ocular adverse events in this clinical trial were dry eye and improper conjunctival closure after the surgical procedure, the latter resulting in exposed implant segments. Exposed segments were treated with revised conjunctival closures. Other ocular adverse events included conjunctival tags, corneal abrasions, conjunctival injection, superficial punctuate keratitis (SPK), conjunctival thinning, and exposed suture. All of these were transient in nature and resolved without sequelae, generally with no or limited medical intervention. IOP increases secondary to postoperative administration of topical steroid drops were reported; in all cases, IOP returned to the baseline level after discontinuation of the steroid drops and/or short-term use of IOP lowering medications in a few cases.

Three (3) cases of decreased iris vascular perfusion resulting in decreased pupil reactivity to light, and iris atrophy were reported in the complete cohort of 858 eyes of this IDE study for an incidence of 0.35%. This adverse event has been mitigated with a high level of standardization of the immediate post-operative surgical protocol to ensure detection of any adverse change in pupil function where recovery falls below minimum standards. In those rare cases, the implant segments will be removed on the day of surgery prior to discharge, thereby reversing any decrease in iris vascular perfusion. All prior cases achieving a measured pupillary response of ≥ 25% constriction by digital infrared pupillometry within 6 hours post-operatively have demonstrated no long-term compromise in pupillary function, nor have they developed any further signs or symptoms of decreased perfusion. Therefore, this protocol will require removal of implant segments on the day of surgery in the rare circumstance that the pupillary constriction does not return to an acceptable level in the immediate postoperative period.

In summary, adverse events were observed in the original IDE study but these were generally mild in nature, self-limiting and largely resolved by 6 months postoperatively. The majority of the adverse events occurred during the early postoperative period, with no serious or significant adverse events observed in the late postoperative period, i.e., at 6 months or later.
7.0 STUDY OUTLINE

7.1 Study Objective
The primary objective of this study is to evaluate the safety and effectiveness of the VisAbility Implant System with the VisAbility Implant, model SGP-046, for improvement in distance corrected near visual acuity (DCNVA) in presbyopic subjects.

7.2 Study Design
This is a prospective multicenter clinical study that will enroll and determine eligible 360 subjects ranging in age between 45 and 60 years of age with distance corrected near visual acuity (DCNVA) and uncorrected near visual acuity (UCNVA) of 20/50 to 20/80 (inclusive). Subjects will be enrolled at up to 14 clinical sites with no site enrolling and determining eligible more than 20% of the 360 eligible subject cohort. A PMA application will be submitted when all study subjects have completed 12 months of follow-up.

Subjects will be consented and screened based on medical history, ocular history and visual acuity criteria. Subjects will be required to satisfy specific inclusion and exclusion criteria during a baseline examination to be eligible for surgery. Subjects will be implanted with the VisAbility Implant in the dominant eye, which will be designated as the primary eye. The fellow eye will be implanted no sooner than 14 days after the primary eye and only in the absence of unresolved adverse events in the primary eye. Subjects primary eye will be examined at one day, one week and at 1, 2, 3, 6, 12, 18 and 24 months post-operatively. The fellow eye will be examined at one day, one week and one month postoperatively. The one week and one month examinations of the fellow eye may be combined with visits for the primary eye if the visit windows permit. After the fellow eye one month visit, the fellow eye will be examined in accordance with the subsequent primary eye examination visits. A validated Patient Reported Outcome Measurement instrument will be given to all enrolled and eligible subjects pre-operatively and at 6, 12, 18 and 24 months.

The study also includes a 60 subject randomized controlled sub-study at 3 investigational sites. Eligible subjects enrolled at these sites will be randomized (1:1 ratio) to a surgery group or a control group. Subjects assigned to the randomized surgery group will be implanted and followed for 24 months in the same manner as the larger non-randomized surgery group. Subjects randomized to the control group will be followed for 6 months, and will be eligible to undergo VisAbility Implant surgery after completion of the six month observation period. These subjects that elect surgery will be followed for 24 months in accordance with the same schedule as the non-randomized surgery group. Randomized control group subjects who do not chose to undergo VisAbility Implant surgery at the end of the 6 month observation period will be exited from the study at that time.

7.3 Effectiveness Endpoint
The primary endpoint is achievement of distance corrected near visual acuity (DCNVA) of Snellen equivalent 20/40 or better (at 40 cm) and at least 10 letters (ETDRS) improvement in DCNVA in the primary eye.

This endpoint will be evaluated against two objectives, a) 75% or more of primary eyes achieve the effectiveness endpoint at 12 months postoperative and, b) the percentage of primary eyes achieving the effectiveness endpoint at 6 months postoperative (6-month responder rate) is higher than the percentage in the randomized control group.
7.4 **Analysis of Safety Data**

Safety data analyses will be performed and separate summaries will be provided for primary and all eyes. Descriptive statistics on the following attributes will be provided:

- BCDVA
- IOP
- Slit Lamp findings
- Fundus exam findings
- Rate of adverse events

7.5 **Study Population**

A total of 360 subjects who meet the following criteria will be enrolled and determined eligible in this study:

7.5.1 **Inclusion Criteria**

1. Subjects must be between ages of 45 to 60 at the time of enrollment.

2. Subjects must have best corrected distance visual acuity (BCDVA) of 20/20 in each eye.

3. Subjects must have distance corrected near visual acuity (DCNVA) @ 40 cm of 20/50, 20/63 or 20/80 in each eye.

4. Subjects must have uncorrected near visual acuity (UCNVA) @ 40 cm of 20/50, 20/63 or 20/80 in each eye.

5. Subjects must have preoperative manifest refraction spherical equivalent (MRSE) in each eye of -0.75 to +0.50 diopters with no more than 1.00 diopter of astigmatism. The difference between the MRSE and cycloplegic refraction spherical equivalent (CRSE) should be ≤0.50 diopter.

6. Subjects must require a minimum add of +1.25 or greater to read 20/20 at near (40 cm).

7. Subjects must be phakic in each eye.

8. Subjects must be alert, mentally competent, and able to understand and comply with the requirements of the clinical study, and be personally motivated to abide by the requirements and restrictions of the clinical study. Patients must be available for the follow-up period.

9. Subjects must be able to provide written informed consent.

7.5.2 **Exclusion Criteria**

1. Subjects where either pupil has a baseline percent change from scotopic to photopic of less than 30% or an absolute difference of less than 1.00 mm between scotopic and photopic pupil size as measured by the NeurOptics Pupillometer.
2. Subjects with ocular inflammation, chronic uveitis, or other recurrent anterior or posterior segment inflammatory conditions in either eye; subjects with any ocular or systemic disease(s) posting a significant risk for ocular inflammation, including but not limited to autoimmune disorders (e.g., rheumatoid arthritis, ankylosing spondylitis, Reiter’s syndrome, ulcerative colitis, Crohn’s disease, psoriasis, sarcoidosis, Behcet’s disease), infections (toxoplasmosis, cat-scratch fever, West Nile virus, syphilis, tuberculosis, herpes zoster, herpes simplex, adenovirus), ocular trauma, or gout.

3. Subjects with scleral thickness of less than 530 microns as measured 3.5 to 4.0 mm posterior to the superior temporal quadrant limbus in either eye.

4. Subjects with a history of any prior intraocular procedure (e.g., corneal transplant, filtering procedures for glaucoma, vitrectomy, retinal detachment repair, cataract surgery) or any prior refractive procedure (e.g. LASIK, surface excimer, or incisional surgery) in either eye.

5. Subjects with any history of prior extraocular muscle surgery or orbital surgery.

6. Subjects with chronic ocular disease, including but not limited to corneal pathology, primary or secondary glaucoma, iritis, herpes simplex, uveitis, trachoma, ocular pemphigoid, Sjogren’s disease, uveal melanoma, Thyroid Related Immune Orbitopathy or clinically significant retinal pathology in either eye.

7. Subjects with any acute ocular disease that has not been completely treated and resolved for at least three months such as conjunctivitis, blepharitis, chalazion, corneal abrasion or keratitis in either eye.

8. Subjects with chronic systemic diseases which may affect the eye, including but not limited to diabetes, ulcerative colitis, systemic lupus erythematosus, Crohn’s disease, collagen vascular disease, rheumatoid arthritis, any bleeding diathesis, or systemic manifestations of HIV/AIDS. Any other uncontrolled systemic disease (e.g., hypertension, cancer, etc.) that could compromise the patient’s participation.

9. Use of any medication, such as coumadin, that could make the surgical procedure more difficult. Subjects using Coumadin, aspirin or NSAID medication under orders from a doctor must be able to provide written approval from the treating doctor for discontinuing this medication at least ten (10) days prior to surgery.

10. Subjects with chronic ocular surface disease, including but not limited to subjects with a prior diagnosis of chronic dry eye syndrome based on tests such as but not limited to, corneal or conjunctival staining, Ocular Surface Disease Index symptom score or Schirmer tear testing.

11. Subjects who are allergic to any medications used in the protocol.

12. Subjects who are pregnant, lactating, or of child-bearing age and not practicing a medically approved method of birth control.
8.0 STUDY METHODS

8.1 Patient Screening and Enrollment

Prior to enrollment in the study, interested subjects will be screened to determine initial eligibility. The investigator or a designee will explain the study purpose and summary procedures and subject responsibilities to the potential subject. If it appears that the subject is interested and may be a candidate for the study, the subject will be asked to review and sign a Screening Informed Consent. The Screening Informed Consent provides a summary of the preliminary screening testing which will include standard of care testing including a medical history, vision testing and an examination of ocular health.

If preliminary eligibility is met, the subject will be asked to sign a Study Informed Consent Form which describes the surgical procedure; the potential benefits and risks, study examinations to be conducted, the frequency of follow-up visits, the expense reimbursement to be provided to the subject as well as other topics. When the Study Informed Consent is signed by the subject and by the Investigator or designee, the Subject is considered to be enrolled. Additional study specific testing of the subject’s ocular and medical condition as specified in the baseline examination will be performed to determine eligibility. If during this testing, the Investigator or Sub-Investigator determines that the subject will not meet the protocol inclusion or exclusion criteria the examination may be terminated.

If the subject satisfies all inclusion and exclusion criteria, the full baseline examination data will be provided to the Sponsor for verification that all data have been obtained and meets eligibility criteria. Upon approval by the Sponsor, the subject will be scheduled for surgery if the subject has been enrolled and determined to be eligible at an Investigational site that is participating in the non-randomized cohort.

If the subject has been enrolled and determined to be eligible at an Investigational site that is participating in the randomized controlled sub-study, the subject will be randomized (1:1 ratio) to either the surgery group or the control group. Subjects randomized to the control group will be followed for 6 months, and will be eligible to undergo VisAbility Implant surgery after completion of the six month observation period.

8.2 Clinical Parameters and Examination Schedule

The clinical parameters to be recorded at baseline and post-operative examinations are shown in Table 1: Schedule of Visits and Measurements on the following page.
## TABLE 1: SCHEDULE OF VISITS AND MEASUREMENTS

<table>
<thead>
<tr>
<th>Pre-Op</th>
<th>0 Day</th>
<th>1 Day</th>
<th>1 Week</th>
<th>1 Month</th>
<th>2 Months</th>
<th>3 Months</th>
<th>6 Months</th>
<th>12 Months</th>
<th>18 Months</th>
<th>24 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slit Lamp Biomicroscopy OD, OS</td>
<td>✓ ²</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Applanation Tonometry OD, OS</td>
<td>✓ ²</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Gonioscopy OD, OS</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Scleral Thickness Measurement OD, OS</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Implant Assessment OD, OS</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Axial Length / ACD OD, OS</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Corneal Topography / Keratometry OD, OS</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pupillometry OD, OS</td>
<td>✓ ²</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Posterior Pole exam with 78/90D lens OD, OS</td>
<td>✓ ²</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Dilated Indirect Ophthalmoscopy 20/30D lens OD, OS</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Visual Fields OD, OS</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cup/Disk Ratio OD, OS</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cycloplegic Refraction w/ VA OD, OS</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Manifest Refraction OD, OS</td>
<td>✓</td>
<td>✓</td>
<td>✓ ⁴</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>BCDVA OD, OS</td>
<td>✓ ²</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>UCDVA OD, OS</td>
<td>✓</td>
<td>✓ ¹</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>UCNVA @ 40 cm OD, OS, OU</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>UCIVA @ 66 cm OU</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>DCNVA @ 40 cm OD, OS, OU</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Patient Preferred Distance DCN - OD, OS, OU UCN - OU</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Minimum add to achieve 20/20</td>
<td>✓</td>
<td>✓</td>
<td>✓ ³</td>
<td>✓ ³</td>
<td>✓ ³</td>
<td>✓ ³</td>
<td>✓ ³</td>
<td>✓ ³</td>
<td>✓ ³</td>
<td>✓ ³</td>
</tr>
<tr>
<td>NAVQ (Validated PRO) &amp; Patient Questionnaire</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Sub-Study Only Wavefront measurements ⁴</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Sub-Study Only Defocus Curve ⁵</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

1. Visual acuity will be measured using pinhole on day 1.
2. Fellow Eye Safety Exam (when fellow eye surgery is 61-180 days after primary eye surgery).
3. Randomized Sub-study subjects only – control group subjects are examined through 6 months and the surgery group through 24 months.
4. Measure BCDVA using baseline refraction.
Examination methods are provided in Appendix 1: Examination Methods.

8.3 Surgical Procedure

The VisAbility Implant System surgical procedure will be performed by the Investigator according to the detailed steps described in Appendix 2: VisAbility Implant System Surgical Procedure. The surgical procedure involves the following basic steps:

• Marking – To indicate the correct rotational position of the VIS Docking Station, two or more drops of xylocaine 2% sterile solution without epinephrine or the equivalent are used topically for anesthesia and marks are made at the 12:00 and 6:00 limbus along the axis of the center of the superior and inferior recti muscle insertions. Additional marking from these two points with the VIS Barrel Marker further aids in VIS Docking Station positioning by providing Vernier visual feedback of proper x/y centering and rotational placement of the VIS Docking Station.

• Peritomy – Additional xylocaine 2% sterile solution without epinephrine or the equivalent is suffused in the anterior subtenon's space for anesthesia. Opening of the conjunctiva and Tenon's capsule at the limbus by standard techniques such as might be used in certain strabismus, glaucoma, or retina surgery is done to provide exposure of the sclera in the area of VIS Docking station fixation points and scleral tunnels. Due to the potential detrimental effect on perfusion and scleral thickness, bipolar and or thermal cautery should not be used during this procedure.

• Placement of the VIS Docking Station – The VIS Docking Station uses a four point fixation system to provide ocular fixation and a fixed docking location for the VIS Scleratome. The VIS Docking Station is centered around the limbus with its internal arrow points on the 6:00 and 12:00 marks and the channels line up with the four radial lines from the VIS Barrel Marker. Each of the four VIS Docking Station's fixation points are then actuated 180 degrees clockwise to its stop. The surgeon should assess fixation and position and correct any deficiency prior to proceeding.

• Scleral Tunnel Creation – The VIS Scleratome locating ridge is docked to the VIS Docking Station channel with the blade guard flush with its corresponding edge. After the footplate is squarely on the sclera, the VIS Scleratome is activated to form each of four scleral tunnels at a fixed position approximately 4mm from the limbus and centered between adjacent recti muscles. USE OF A MANUAL LAMELLAR BLADE IS NOT ALLOWED FOR USE IN CREATING OR AUGMENTING ANY SCLERAL TUNNEL.

To minimize manipulation of the eye, a VisAbility Implant Segment should be placed in each Lamellar Scleral Tunnel made prior to proceeding to the creation of the next Lamellar Scleral tunnel.
8.4 Post-Operative Care

Following surgery, physicians should adhere to the following guidelines of topical ophthalmic medications and care:

- To help control pain postoperatively, an icepack should be applied to the eye at intervals for approximately 30 minutes or longer as needed. A topical non-steroidal anti-inflammatory drug (NSAID) such as nepafenac ophthalmic suspension or equivalent may also be instilled immediately postoperatively. Chilled BSS may be instilled every 15 minutes and topical steroid drops such as prednisolone acetate 1% ophthalmic suspension or equivalent may be used every 15 to 30 minutes until the pupil reaction is greater than 25% as described in the next step. Prior to discharge the patient should be given Diamox 500mg Sequel PO or equivalent.
• Pupil functionality will be evaluated postoperatively using a NeurOptics Pupillometer every 15 to 30 minutes until the percent pupil constriction reading is at least 25%. A second, confirmatory reading may be taken as soon as 5 minutes after the first. If two pupil constriction readings of at 25% or greater are not achieved within the first 4 hours after surgery, preparation for removal of the implant segments will commence. The Investigator must remove all four implant segments no later than 6 hours after the surgery if two pupil constriction readings of 25% or greater are not achieved within 6 hours postoperatively.

• During the first week after the surgery, antibiotic drops such as moxifloxacin ophthalmic solution or equivalent and a topical steroid such as Lotemax gel or equivalent should be instilled in the eye. Additionally, NSAIDs such as topical nepafenac ophthalmic suspension or equivalent and / or oral medications such as naprofen or equivalent or acetaminophen with codeine or equivalent may be given as needed for pain during this time.

• Absorbable and / or non-absorbable conjunctival sutures may be removed at one week post-operatively or later as needed.

8.5 Scheduled Post-Operative Visit Schedule

8.5.1 Primary Eye Visit Schedule

Subjects enrolled and eligible in the non-randomized cohort of the study and subjects enrolled, eligible and assigned to the randomized surgery group will be examined according to the following schedule based on the date of primary eye surgery. Surgery on the primary eye may not occur more than 60 days after a baseline examination establishing eligibility. Visit windows are calculated on a 30 day month.

<table>
<thead>
<tr>
<th>Visit Type</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-operative Baseline Evaluation</td>
<td>(Day -60 to Day -1)</td>
</tr>
<tr>
<td>Surgery</td>
<td>(Day 0)</td>
</tr>
<tr>
<td>One Day Exam</td>
<td>(18 to 36 hours)</td>
</tr>
<tr>
<td>One Week Exam</td>
<td>(7 days +/- 2 days)</td>
</tr>
<tr>
<td>One Month Exam</td>
<td>(1 month +/- 7 days)</td>
</tr>
<tr>
<td>Two Month Exam</td>
<td>(2 months +/- 14 days)</td>
</tr>
<tr>
<td>Three Month Exam</td>
<td>(3 months +/- 14 days)</td>
</tr>
<tr>
<td>Six Month Exam</td>
<td>(6 months +/- 21 days)</td>
</tr>
<tr>
<td>Twelve Month Exam</td>
<td>(12 months +/- 45 days)</td>
</tr>
<tr>
<td>Eighteen Month Exam</td>
<td>(18 months +/- 45 days)</td>
</tr>
<tr>
<td>Twenty-four Month Exam</td>
<td>(24 months +/- 60 days)</td>
</tr>
</tbody>
</table>
8.5.2 Subjects Randomized to the Control Group – Visit Schedule

Subjects enrolled, eligible and assigned to the randomized control group will be examined within the visit windows according to the following schedule.

- **Enrollment Randomization** (Day 0)
- **Three Month Exam** (3 months +/- 14 days)
- **Six Month Exam** (6 months +/- 21 days)

Subjects in the randomized control group that have completed the 6 month follow-up exam may elect to undergo placement of the VisAbility Implant. For these subjects, the 6 month visit will serve as the baseline eligibility examination. Subjects that undergo surgery will be examined in accordance with the primary eye visit schedule shown above.

8.5.3 Fellow Eye Visit Schedule

Subjects undergoing surgery in the fellow eye will be examined according to the following visit schedule. The one week and one month examinations may be combined with visits for the primary eye if the visit windows permit. After the one month visit, the fellow eye will be examined at the same time as scheduled follow-up visits for the primary eye.

- **Surgery** (Day 0)
- **One Day Exam** (18 to 36 hours)
- **One Week Exam** (7 days +/- 2 days)
- **One Month Exam** (1 month +/- 14 days)

If the fellow eye surgery is 61 to 180 days after the primary eye surgery, the fellow eye will be examined postoperatively after the one month visit, on a separate visit schedule for the 3 and 6 month visits only, established based on the same intervals and visit windows as shown above for the primary eye. Subsequent to the 6 month visit, the fellow eye will be examined at the same visit as the primary eye. Fellow eye and OU data will be recorded as attributable to the fellow eye visit timing through the fellow eye 6 month postoperative visit.

8.5.4 Fellow Eye Supplemental Baseline Examination

Fellow eye surgery may be performed 61 to 180 days after the baseline examination that has determined eligibility if a safety exam is performed and the findings do not alter the subject’s continued eligibility. The following clinical parameters will be evaluated in the safety exam:

1. Medical history
2. BCDVA
3. Slit lamp biomicroscopy
4. Goldmann tonometry
5. Pupillometry
6. Posterior pole examination.
If fellow eye surgery is to be performed 181 days or more after a baseline exam determining eligibility, a complete baseline examination must be repeated. Baseline efficacy data for the fellow eye and for OU will always be from the baseline examination established prior to the primary eye surgical intervention.

8.5.5 Long-Term Follow-Up

Long-term follow-up (up to an additional 3 years beyond the end of this study) may be required by the FDA for this study. If required study participants will be examined according to the following schedule based on the primary eye surgery if they choose to participate,

- Thirty-six Month Exam (36 months +/- 60 days)
- Forty-eight Month Exam (48 months +/- 60 days)
- Sixty Month Exam (60 months +/- 60 days)

The clinical parameters to be recorded for these long-term follow-up examinations will be established in accordance with the FDA’s requirements.

8.6 Data Collection

Sample paper source documents will be provided by the Sponsor for each subject enrolled and determined eligible in the study and will be completed by the Investigator or Sub-Investigator at the time of the subject examination. The source documents will be completed in a clear and legible manner in black or blue ink and then signed and dated by the Investigator as indicated on the form. Any correction will be made by drawing a single line through the incorrect entry, adding the correct entry, and then initialing and dating the corrected entry.

The information recorded on the source documents will then be entered into the electronic case report form (eCRF) in the Electronic Data Capture (EDC) System by the Investigator, Sub-Investigator or designee. The original dated and signed source document will be kept in the subject’s study file at the Investigator’s site. Instructions for the entry of data into the EDC will be provided to the clinical sites.

8.7 Study Completion

Subjects are considered to have completed the study when they complete the 24 month exam regardless of earlier missed visits. The length of participation of subjects in the study is as follows.

- Subjects enrolled and eligible in the non-randomized surgery cohort and subjects that are enrolled and eligible in the randomized surgery group as part of the randomized sub-study will participate in the study for 24 months.
- Subjects enrolled and eligible in the control group of the randomized sub-study who elect not to undergo surgery will participate in the study for 6 months.
- Subjects enrolled and eligible in the control group of the randomized sub-study who elect to undergo surgery after 6 months in the observation period will participate in the study for 30 months.
8.8 Subject Termination or Withdrawal

Subjects may be terminated from the study if the Investigator believes that continued participation in the study may jeopardize the subject’s health or welfare. Subjects may also elect to withdraw from the study at their discretion. Every effort will be made to encourage the subject to maintain compliance with the protocol and to continue in the study. Further, every effort will be made in both instances to conduct examinations as determined by the Investigator to ensure the safety of the subject. The Sponsor should be notified promptly by the Investigator upon the termination or withdrawal of a subject by completion of the Study Exit form. Terminated or withdrawn subjects may not be replaced with additional enrolled and eligible subjects. Subjects who have all implant segments removed (explanted) from both eyes will be exited from the study after at least 3 months post-explant follow-up.
9.0 INVESTIGATIONAL MATERIALS

The investigational materials provided for the clinical study of the VisAbility™ Implant System include the following:

- VisAbility Implant
- VisAbility Incision System:
  - VIS Scleratome
  - VIS Docking Station
- VIS Feeder Tube and VIS Shuttle
- VIS Instrument Set

9.1 VisAbility Implant Segment

The VisAbility Implant is a curved scleral implant segment that is injection molded from polymethylmethacrylate (PMMA), a material with an extensive history of long-term implantation in the human eye, including intraocular lenses (IOLs). Four (4) VisAbility Implant segments are placed in a single presbyopic eye to improve near vision.

Each VisAbility Implant segment consists of 2 pieces, a main body with 2 legs and a center insert. The center insert has transverse longitudinal grooves on both sides that correspond to 2 small "rails" on the interior edges of the legs of the main body (Figure 1). These features allow the insert to be smoothly snapped into place in the main body.

The design of the VisAbility Implant segments includes stabilization feet at each end intended to fixate at the entrance and exit sides of the scleral tunnel incision, thereby preventing displacement or migration of the implanted VisAbility Implant segments. The VisAbility Implant segments are provided sterile in a Tyvek® peel pouch.

Figure 1: VisAbility Implant Segment showing 2 interlocking pieces and stabilization feet.
The VisAbility Incision System consists of the specialized surgical instruments provided to create precisely positioned scleral tunnels:

- **VIS Scleratome**
- **VIS Docking Station**

### 9.2.1 VIS Scleratome

The VIS Scleratome (Figure 3) is a custom designed disposable Scleratome used to create the scleral tunnel incisions into which the VisAbility Implant segments are placed. The VIS Scleratome is designed to create consistent scleral tunnel incisions for implantation of the VisAbility Implant segments. Ultrasound imaging is performed as part of the patient screening examination to confirm that the thickness of the sclera in the region of placement of the VisAbility Implant segments satisfies the requirements for making the scleral incisions. The VIS Scleratome is provided sterile in a disposable plastic tray with a Tyvek® cover and is for single patient use only.

### 9.2.2 VIS Docking Station

The VIS Docking Station (Figure 4A and 4B) is a template made of titanium and medical grade stainless steel that is temporarily fixated on the eye centered around the geometric corneal limbus to provide a guide for placement of the VIS Scleratome. The VIS Scleratome docks with the VIS Docking Station to provide a consistent location for the scleral tunnel incisions (Figure 5A and 5B).
When the VIS Docking Station is placed on the eye, a point on the VIS Docking Station is positioned to align with the 6:00 and 12:00 o'clock hour marks on the patient's limbus (Figure 4) corresponding to the radial center of the inferior and superior recti muscles. The surgeon is then able to verify that the VIS Scleratome docking channels in the oblique quadrants are properly located between the rectus muscles. The VIS Docking Station is then temporarily fixated to the eye with 4 titanium double helix twist picks. The VIS Scleratome is then docked, 1 quadrant at a time, into each of the channels located at the 1:30, 4:30, 7:30, and 10:30 clock positions of the VIS Docking Station. The VIS Scleratome is docked using the "locating ridge" on the blade guard of the Scleratome (see Figure 5).

Actuate the Scleratome by turning the integrated winding knob in the clockwise direction. After placing the VIS Scleratome in position on the sclera using the VIS Docking Station, the actuator button on the Scleratome handle is pressed, releasing and retracting the blade and creating the scleral tunnel. The Scleratome is then reloaded for the next actuation by turning the integrated winding knob in the clockwise direction.

The VIS Docking Station is a reusable instrument that can be sterilized by standard autoclave procedures. It is provided in a plastic case along with the other reusable surgical instruments. Directions for cleaning and autoclave sterilization of the VIS Docking Station and the other reusable surgical instruments are provided to the surgeon.

9.3 VIS Feeder Tube and VIS Shuttle

After the scleral tunnels have been formed, the VisAbility Implant segments are inserted using the VIS Feeder Tube and VIS Shuttle. The VIS Feeder Tube is made of PTFE (Teflon), a commonly used medical grade polymer. The soft, lubricious and flexible PTFE tubing provides the optimal means of traversing the lamellar scleral tunnel with the least amount of external stress on surrounding tissue. Each VisAbility Implant main body can be loaded into a VIS Feeder Tube by the surgical assistant prior to transport from the assistant's sterile workspace to the surgeon for implantation.
The VIS Shuttle is a titanium instrument consisting of 2 sections: a trailing section, cylindrical in shape, which is inserted into the tubing of the VIS Feeder Tube, and a leading section that tapers from the tubing outer diameter down to a dull round tip to facilitate positioning into the scleral tunnel.

The VIS Shuttle is inserted into the larger end of the VIS Feeder Tube. The main body of the VisAbility Implant segment is compressed into the other end. The VIS Shuttle is then passed through the scleral tunnel, pulling with it the VIS Feeder Tube with the compressed main body of the VisAbility Implant segment. As the tube exits the tunnel, the trailing stabilization feet on the legs of the implant catch the entrance of the tunnel and hold it in place as the tubing is removed, and the forward locking stabilization feet open to engage the exit incision. Final assembly of the implant follows, as the center insert is positioned and snapped into place creating a single VisAbility Implant segment.

Figure 6 shows how the VisAbility Implant main body is used with the VIS Feeder Tube and VIS Shuttle. Figures 7A, 7B and 7C shows how the VIS Feeder Tube and VIS Shuttle are used to place the VisAbility Implant segments in the scleral tunnel.
The VIS Feeder Tubes are provided sterile in a Tyvek® peel pouch. The VIS Shuttle is a reusable component that can be sterilized by standard autoclave procedures. Four (4) VIS Shuttles are provided in a plastic case along with the other reusable surgical instruments. Directions for cleaning and autoclav e sterilization of the VIS Shuttles and the other reusable surgical instruments are provided to the surgeon.

9.4 VIS Instrument Set

The VIS Instrument Set contains an array of Class 1 reusable manual surgical instruments, including the VIS Docking Station and the VIS Shuttles. All of these instruments are manufactured from 6Al 4V titanium alloy and/or medical grade stainless steel materials that have a lengthy history of safe use in ophthalmic surgical procedures. These instruments are provided non-sterile in a plastic case. They may be sterilized by standard autoclaving procedures and are provided with instructions for cleaning and sterilization.

9.5 VisAbility Implant Removal

In the event that VisAbility Implant segments require removal, this can be accomplished easily by utilizing the VisAbility Implant Removal Cutter instrument provided in the VIS Instrument Set to remove the locking barbs from solid end of the VisAbility Implant segment, then using forceps to withdraw the remaining implant segment through the scleral tunnel (Figure 8A, 8B and 8C).

FIGURE 8A, 8B AND 8C: VISABILITY IMPLANT REMOVAL PROCEDURE
10.0 ADVERSE EVENT REPORTING

An Adverse Event (“AE”) is any untoward sign, symptom or disease observed during the course of the study regardless of the suspected cause. Conditions or diseases that are pre-existing or chronic but stable are not Adverse Events. Changes in pre-existing or chronic conditions or diseases that are consistent with natural disease progression are not Adverse Events.

10.1 Serious Adverse Events (SAE)

An Adverse Event should be classified as a Serious Adverse Event (“SAE”) and reported as such, if it meets one or more of the following criteria:

- It results in death (i.e., the Adverse Event actually causes or leads to death).
- It is life threatening (i.e., the Adverse Event places the subject at immediate risk of death).
- It is considered sight-threatening (i.e., the Adverse Event involves loss of vision at the time of diagnosis and carries a relatively grave prognosis of irrevocable loss of vision without timely high risk intervention).
- It requires or prolongs inpatient hospitalization (i.e., the Adverse Event requires at least a 24-hour inpatient hospitalization or prolonged hospitalization beyond the expected length of stay) Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions are not SAEs.
- It results in persistent or significant disability/incapacity (i.e., the Adverse Event results in substantial disruption of the subject’s ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- It does not meet any of the above serious criteria but may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

If a subject is hospitalized to undergo a medical or surgical procedure as a result of an Adverse Event, the event responsible for the procedure, not the procedure itself, should be recorded as the event. (For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass).

Investigators must notify Refocus of any SAE within 24 hours of observing or learning of the event. For initial SAE reports, Investigators should record all case details that can be gathered within 48 hours on the SAE Form and fax immediately upon completion to Refocus.

10.2 Unanticipated Adverse Device Effects (UADE)

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life-threatening or sight-threatening problem or death caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence. UADEs also include any unanticipated sight-threatening events and any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Investigators must notify Refocus of any UADE within 24 hours of observing or learning of the event. Refocus will be responsible for informing Regulatory Authorities and all other IRBs and Investigators participating in the study of the UADE.

10.3 Adverse Event Assessment

All subjects who have been exposed to the study treatment will be evaluated for Adverse Events as defined in this protocol. All adverse events, regardless of severity and whether or not they are ascribed to the study treatment, will be recorded in the source documents using standard medical terminology. Pre-existing conditions or diseases present at baseline that remain stable or change in a manner consistent with natural disease progression are not considered Adverse Events.

All Adverse Events will be evaluated beginning at the time of onset, and evaluation will continue until resolution or until the investigator determines that the subject’s condition is stable. The investigator will take appropriate and necessary therapeutic measures required for resolution of the Adverse Event. Any medication necessary for the treatment of an Adverse Event must be recorded on the concomitant medication source document.

All AEs will be characterized by the following criteria:

- Event term
- Intensity or severity
- Expectedness
- Relationship to study treatment
- Outcome
- Treatment or action taken.

Whenever possible, recognized medical terms should be used when recording AEs. Colloquialisms and/or abbreviations should not be used. Only one medical concept, preferably a diagnosis instead of individual symptoms, should be recorded as the event.

If known at the time of reporting, a diagnosis (i.e., disease or syndrome) should be recorded on the source document rather than individual signs and symptoms (e.g., record congestive heart failure rather than dyspnea, rales, and cyanosis). If a constellation of signs and/or symptoms cannot be characterized with a single medical diagnosis or syndrome and they are considered unrelated to an encountered syndrome or disease at the time of reporting, these individual events should be recorded as separate AEs (e.g., if congestive heart failure and severe headache are observed at the same time, each event should each be recorded as an individual AE). If a diagnosis was not initially reported, and is subsequently established it should be reported as follow-up information and the original AE documents updated accordingly.

Adverse Events occurring secondary to other events (e.g., sequelae) should be identified by the primary cause; a "primary" event, if clearly identifiable, should represent the most accurate clinical term to record as the AE event term. For example:

*Orthostatic hypotension* ⇒ *fainting and fall to floor* ⇒ *head trauma* ⇒ *neck pain*

The primary event is orthostatic hypotension and the sequelae are head trauma and neck pain.
10.4 Classification of Adverse Events by Intensity / Severity

All Adverse Events should be graded on a four-point scale (mild, moderate, marked, severe) for intensity/severity. These definitions are as follows:

**Mild:** Transient discomfort; no medical intervention/therapy required and does not interfere with daily activities.

**Moderate:** Low level of discomfort or concern with mild to moderate limitation in daily activities; some assistance may be needed; minimal or no medical intervention/therapy required.

**Marked:** Considerable discomfort with limitation in daily activities, some assistance usually required; medical intervention/therapy usually required.

**Severe:** Extreme discomfort and limitation in daily activities, significant assistance required; **significant** medical intervention/therapy required.

There is a distinction between the severity and the seriousness of an Adverse Event. Severity is a measurement of intensity; thus a severe reaction is not necessarily a Serious Adverse Event. For example, a headache may be severe in intensity, but would not be serious unless it met one of the criteria for Serious Adverse Events.

10.5 Classification of Adverse Events by Expectedness / Relatedness

All AEs will be evaluated as to whether they are expected or unexpected, as defined below:

**Expected (anticipated):** An Adverse Event is expected when the nature, severity, or degree of incidence was previously described.

**Unexpected (unanticipated):** An Adverse Event is unexpected when the nature, severity, or degree of incidence was not previously described.

All AEs will be evaluated as to whether they are related to the device, as defined below:

**Not Related:** Strong evidence exists that the Adverse Event definitely has a cause other than the investigational device (e.g. pre-existing condition or underlying disease, concurrent illness, or concomitant medication), or the investigational device cannot be implicated based on the available information

**Possibly Related:** There is a temporal association with the investigational device and it cannot be excluded as a cause but other etiologies are also likely to be the cause based upon available information

**Probably Related:** There is a temporal association with the investigational device which makes a causal relationship probable where other etiologies are possible but unlikely to be the cause, based upon available information.

**Definitely Related:** Strong evidence exists that the investigational device definitely caused the Adverse Event. There is a temporal relationship between the event onset and the investigational device and the subject’s clinical state and concomitant therapies have
been ruled out as a cause, based upon available information.

10.6 Adverse Event Outcome
The clinical outcome of an Adverse Event will be recorded and characterized as follows:

- Resolved without sequelae
- Resolved with sequelae (specify)
- Ongoing (i.e. continuing at time of study discontinuation)
- Death.

10.7 Treatment or Action Taken
The clinical treatment of an Adverse Event will be documented and characterized as follows:

- None
- Medical Intervention
- Surgical Intervention
- Other

10.8 Anticipated Adverse Events
Adverse Events that might reasonably be expected to occur in this study are listed below. The time periods refer to the exam visit that occurs corresponding to the post-operative follow-up visit schedule (i.e., 3 months means the 3 month postoperative visit). Exams for the primary eye and fellow eye may be done at the same visit if windows permit. For purpose of determining whether a fellow eye event is an Adverse Event, the time period used shall be based on the date of the fellow eye surgery.

These specific examples of anticipated Adverse Events include, but are not limited to:

**Intraoperative Events**
- Scleral perforation
- Scleral perforation with vitreous prolapse

**Lids and Lashes**
- Ptosis
- Onset of or worsening to severe clinically significant lid margin disease (e.g., blepharoconjunctivitis, blepharitis, meibomitis, meibomian gland dysfunction, etc.) after 3 months postoperative

**Cornea**
- Corneal dellen after 1 week postoperative
- Corneal abrasion > 2mm after 1 week postoperative
- Dry eye signs (moderate or severe) of corneal and/or conjunctival staining, etc., requiring prescription medication after 6 months postoperative
- Corneal edema (moderate or severe) after 1 month postoperative
- Corneal infiltrate or ulcer
Conjunctiva/Sclera

- Conjunctival cyst
- Conjunctival thinning or erosion
- Moderate or severe conjunctival injection at 3 months postoperative or later
- Subconjunctival hemorrhage after 3 months postoperative

Anterior Segment, Iris, Lens

- Pupil abnormalities persisting after 3 months
- Grade 4 anterior segment ischemia (corneal edema, anterior chamber reaction, and decreased pupil reactivity)*
- Anterior chamber cells or flare greater than mild at Day 1 through 1 Week
- Anterior chamber cells or flare after 1 week postoperative
- Intraocular Inflammation other than anterior chamber cells and flare (e.g., vitritis)
- Two grade change in lens opacity compared to baseline on two consecutive post-operative visits
- Displaced or missing implant segments

Intraocular Pressure

- Hypotony (IOP < 6mmHg)
- Increase in IOP of > 10mm Hg over baseline or IOP > 30mm Hg at two consecutive visits at 1 week or later

BCDVA Loss

- Decrease in BCDVA of greater than or equal to 2 lines (≥10 letters ETDRS) at 3 months or later

Fundus

- Choroidal effusion
- Retinal detachment
- Retinal or vitreous hemorrhage

Secondary Surgical Intervention

- Implant segment removal
- Exposed implant segments or conjunctival retraction requiring conjunctival re-approximation

Other

- Eye pain requiring oral prescription pain medication after 1 week postoperative
- Allergic reactions to medications, devices, sutures or anesthesia
- Other findings worsening two grades from baseline to a grade of +3 or +4

* Refer to Appendix 6: Anterior Segment Ischemia (ASI): Detection, Mitigation and Reporting
11.0 STATISTICAL METHODS

This is a prospective, multicenter study with a randomized, controlled sub-study that is designed to evaluate the safety and effectiveness of the scleral implant procedure. The percentage of primary eyes achieving the effectiveness endpoint will be evaluated at 12 months postoperatively. Within the study cohort, a subgroup will be randomized on a 1:1 ratio to a surgery group and a control group. Subjects in the randomized control group will not receive surgery and will be examined at 3 months and 6 months. After completion of the 6 month observation period, subjects in the randomized control group will be eligible to receive surgery as part of the 360 subject cohort. This randomized controlled sub-study will be used to evaluate the effectiveness of the scleral implant procedure in the randomized surgery group compared to effectiveness in the randomized control group at 6 months postoperatively.

The effectiveness endpoint, hypotheses, sample size calculations, analysis population, handling of missing data, analysis methods, and analysis of safety data are as follows.

11.1 Effectiveness Endpoint

The effectiveness endpoint is:

Achievement of distance corrected near visual acuity (DCNVA) of Snellen equivalent 20/40 or better (at 40 cm) and at least 10 letters (ETDRS) improvement in DCNVA in the primary eye.

11.2 Statistical Hypotheses

For the effectiveness endpoint, two objectives must be met.

**Objective #1:**
The scleral implant procedure is defined as successful if 75% or more of primary eyes achieve the effectiveness endpoint at 12 months postoperative. The corresponding statistical hypothesis is as follows:

\[ H_0 \text{ (null hypothesis): } \ p < 0.75 \]
\[ H_a \text{ (alternative hypothesis): } \ p \geq 0.75 \]

Where, \( p \) is the probability that subjects achieve the effectiveness endpoint at 12 months postoperative (12-month responder rate).

**Objective #2:**
An analysis of the randomized surgery group and randomized control group will be conducted. The randomized surgery group is defined as successful if the percentage of primary eyes achieving the effectiveness endpoint at 6 months postoperative (6-month responder rate) is higher than the percentage in the randomized control group. The corresponding null and alternative hypotheses are as follows:

\[ H_0 \text{ (null hypothesis): } \ p_1 \leq p_2 \]
\[ H_a \text{ (alternative hypothesis): } \ p_1 > p_2 \]

Where:
- \( p_1 \) is the percentage of primary eyes in the randomized surgery group who achieve the effectiveness endpoint at 6 months.
- \( p_2 \) is the percentage of primary eyes in the randomized control group who achieve the effectiveness endpoint at 6 months.

The primary eye is defined as the subject's dominant eye and the eye that will undergo surgery first. It is intended that all subjects will also undergo surgery in the fellow eye at a subsequent date as specified in the protocol.

11.3 Sample Sizes

Both Objective #1 and #2 will need to be statistically significant in order to determine the effectiveness of the study device. Therefore the two-sided significance level of 0.05 is not adjusted for the multiplicity.

Full Study Cohort Effectiveness Endpoint

The sample size calculation for the statistical hypotheses described for Objective #1 in Section 11.2 is based on the following criteria:

- The two-sided significance level = 0.05 (or one-sided significance level = 0.025).
- The statistical power = 90\% at \( p = 0.825 \). The assumption of true responder rate of 0.825 is based on the simple average of success rate observed in previous Refocus clinical study data, as follows:
  - Disposable Scleratome group had an observed success rate of 88\%.
  - Re-usable Scleratome group had an observed success rate of 77\%.
  - Simple average of 88\% and 77\% is 82.5\%.
- Binomial distribution is used for sample size calculation.

Based on the criteria above for Objective #1, 330 treated primary eyes should be available for analysis at 12 months. If a dropout rate of 10\% of subjects by 12 months is considered, then the surgery cohort should include approximately 360 treated primary eyes.

For safety analysis, in order to detect an Adverse Event (AE) with a true probability of occurrence among subjects of 1\% with 95\% probability, based on the binomial distribution, a sample of at least 299 eyes would be required (in accordance with ANSI Z80.29 18Nov2013 AIOL [rev20]). Assuming a drop-out rate of approximately 10\% of subjects by 12 months, the surgery cohort should include a minimum of 333 treated primary eyes.

A sample size of 333 treated primary eyes will meet the sample size requirements for both safety and effectiveness. The study cohort is planned for 360 surgery subjects at up to 14 study sites. However, no site may enroll and determine to be eligible more than 20\% of the subject surgery cohort.

Randomized Sub-study

The sample size for Objective #2 in Section 11.2 is based on the following criteria:

- The two-sided significance level = 0.05 (or one-sided significance level = 0.025).
• Based on the randomized control group data collected in IDE G970152, the 6-month responder rate is estimated as 10% for the control group.

• Based on the surgery group data collected in IDE G970152, the 6-month responder rate was lower than the 12-month responder rate. Therefore, it is assumed that the 6-month responder rate of the randomized surgery group in this study will be approximately 0.75.

• The statistical power = 90%.

• Fisher’s exact test is used for sample size calculation.

Based on the criteria above, a sample of 14 randomized surgery group primary eyes and 14 randomized control group primary eyes at 6 months will ensure a power greater than 90% for Objective #2, using a one-sided alpha of 0.025.

A sample size of 30 randomized surgery group subjects and 30 randomized control group subjects has been selected which will account for a possible 10% subject drop-out rate and allow for greater accuracy in point estimates for both groups. This randomized sub-study will be conducted at 3 clinical sites. Sites will be chosen based on availability of equipment for additional sub-study measures, such as availability of an iTrace unit (Tracey Technologies, Houston, TX), and the ability and willingness of the site to participate in the additional sub-study. The target enrollment at each of the 3 sites in the randomized sub-study will be 20 eligible subjects to provide an even distribution. However, no site may enroll and determine eligible more than half of the randomized sub-study cohort or 30 subjects.

11.4 Cohort Population

Potential subjects will sign a screening consent to undergo preliminary screening for eligibility that consists of standard of care eye examinations. Subjects who may be eligible based on the preliminary screening criteria and are willing to participate in the study will sign a full informed consent and are considered enrolled. At that time, the study specific examinations required to complete the baseline examination will be administered to determine eligibility for the study. Subjects who have signed the full informed consent but do not meet all of the inclusion and exclusion criteria will be considered enrolled but ineligible for the study. The reason for the disqualification will be recorded and reported.

Safety Cohort: All eyes (both primary and fellow eyes) that have undergone surgical preparation of the ocular surface.

Effectiveness Cohort: All primary eyes that have been implanted with at least one implant segment and primary eyes of subjects that have been enrolled and determined eligible in the randomized control group.

Figure 9, below, summarizes the status of enrolled subjects and the cohort populations for the study, except that the randomized control group is not shown.
Study Population and Subject Accountability

- # of Subjects Who Sign Screening Consent
  - # of subjects that do not meet initial eligibility
  - # of Subjects Who Sign Consent
    - # of subjects that do not meet inclusion/exclusion criteria (enrolled and ineligible)
    - # of Eyes # of Subjects Eligible and Enrolled
      - # of subjects not undergoing surgical preparation of the ocular surface
        - Safety Cohort All Eyes
          - Primary Safety Endpoint
            - 12 month visit data
          - # of operated Primary Eyes without implantation of at least one implant segment
            - Effectiveness Cohort Primary Eyes
              - Primary Effectiveness Endpoint
                - 12 month visit data

**Figure 9 – Illustration of Study Population and Accountability**
11.5 Subject Accountability

The following terms and definitions will be used for the accountability of the study population and are based on the definitions found in ANSI Z80.29 Rev 018, section B.5.3 as modified and explained below.

- Enrolled – the total number of subjects that have signed the full informed consent.
  - Enrolled but ineligible – the total number of subjects that have signed the full informed consent but do NOT meet all of the inclusion/exclusion criteria.
  - Enrolled and eligible – the total number of subjects that have signed the full informed consent and meet all of the inclusion/exclusion criteria.

- Surgical Withdrawal – Subjects (eyes) that have been enrolled and determined eligible but do not undergo surgical preparation of the ocular surface for any reason.

- Discontinued – Subjects (eyes) that have discontinued treatment prior to the visit window associated with the form as a result of death, the removal of all 4 implant segments (explant), or any other reason except lost to follow-up.
  - Explanted Eye – Eyes that underwent implantation surgery, but have had all implanted segments removed.

- Lost to Follow-up – Subjects that have withdrawn from the study after initial eye surgery or subjects that have missed the visit window associated with the form and all subsequent scheduled visits despite documented efforts by the Investigator to schedule the subject for follow-up.

- Missed Visit – Data for subjects (primary eyes) that is not available for a follow-up visit within the specified visit window associated with the form, but data is available for a subsequent follow-up visit for such subject.

11.6 Analysis of Effectiveness Cohorts

For the primary analysis of Objective #1, all observed 12-month data of the surgical primary eyes will be included in the effectiveness analysis. Missing data will not be imputed except that explanted primary eyes will be imputed as failures.

For the primary analysis of Objective #2, all reported 6-month data of the randomized primary eyes will be included in the analysis. Missing data will be imputed as follows:

- Randomized Control Group: In the absence of 6 month visit data, the nearest available data recorded between and including the 3 month visit up to the 6 month visit will be utilized. Since this randomized control group does not receive the benefit of the surgery during this 6 month observation period, the lost to follow-up and missed visit rate could be higher and since no intervention occurs during the 6 month period, this imputation of missing data is warranted. In the absence of any observed data between the 3 month visit
and 6 month visit, this missing data will not be imputed since failure to achieve the effectiveness endpoint is expected.

- **Randomized Surgery Group:**
  - Explanted primary eyes will be imputed as failures.
  - In the absence of 6 month visit data, the nearest recorded data after 6 months up to and including 12-month visit data will be used. This imputation is warranted as the visit data between 6 and 12 months provides a predictive indicator of 6 month results. In the absence of any observed data between 6 and including 12 months, this other missing data will not be imputed.

### 11.7 Baseline Demographic Characteristics

Demographic data including, but not limited to, age, race, sex and ethnicity and baseline characteristics including, but not limited to, DCNVA, UCNVA, UCDVA, BCDVA, manifest refraction spherical equivalent (MRSE), cycloplegic refraction spherical equivalent (CRSE), will be reported for each subject. Baseline characteristics such as age, sex, race, and near visual acuity will be summarized.

### 11.8 Analysis of Effectiveness Data

As noted previously, both Objective #1 and Objective #2 of the primary effectiveness endpoint must be satisfied in order for the study to be considered a success.

**Analysis of Objective #1:**

The one-sided 97.5% lower confidence limit of the 12-month responder rate will be calculated based on the exact binomial distribution. This goal is met if the one-sided 97.5% lower confidence limit of the 12-month responder rate is at least 75%.

The percentage of primary eyes achieving the Effectiveness Endpoint at 12 months will be compared among the study sites. The Fisher’s exact test will be used to evaluate the possible study site effect. If the site effect is significant, i.e., p-value ≤ 0.15, then 12-month responder rates stratified by study site will be provided and the average of the site 12-month responder rates will be calculated. The normal distribution approximation will be used to estimate the one-sided lower 97.5% confidence limit for the average 12-month responder rate.

Fisher’s exact test will also be used to assess the effects of subject sex, race and age category at surgery on the 12-month responder rates for primary eyes using a p-value of 0.15. For this analysis, age will be categorized into 3 interval groups (i.e., 45-49, 50-54, and 55-60).

**Analysis of Objective #2:**

The number and percentage of primary eyes achieving the Effectiveness Endpoint at 6 months will be summarized for the randomized surgery group and randomized control group separately. The two-sided Fisher’s exact test will be used to compare the difference between 6-month responder rates of the two randomized groups.
In order to assess potential differences of randomized group allocation and/or site 6-month responder rates, a logistic regression analysis examining with the following will be performed:

- treatment effect (the randomized surgery group and the randomized control group at that same site),
- study site effect (site by site success rate comparison), and
- site by treatment interaction

If there is a significant difference ($p \leq 0.15$) in treatment effect, study site effect, or a significant interaction effect between study site effect and treatment effect ($p \leq 0.15$), then the 6-month responder rate for each study group and the difference in the 6-month responder rate between the two randomized groups ($p_{\text{treatment}} - p_{\text{deferred}}$) will be summarized by each study site.

**Sensitivity Analysis of Objective #1:**

Sensitivity analysis will be performed for Objective #1 using the following imputation methods for missing 12-month data:

- **Best Case Analysis:** All discontinued primary eyes will be imputed as effectiveness failures. For primary eyes lost to follow-up or for primary eyes missing 12-month visit data, the best value from any protocol scheduled visit at 1 month or later (1 month, 3 month or 6 month visit) will be used. If such visit data does not exist for a primary eye, the effectiveness will be imputed as a success.

- **Worst Case Analysis:** All discontinued primary eyes will be imputed as effectiveness failures. For primary eyes lost to follow-up or missing 12 month visit data, the worst value from any protocol scheduled visit at 1 month or later (1 month, 3 month or 6 month visit) will be used. If such visit data does not exist for a primary eye, the effectiveness will be imputed as a failure.

- **Tipping Point Analysis:** All discontinued primary eyes will be imputed as effectiveness failures. For primary eyes missing 12-month visit data for reasons other than discontinued, effectiveness will be initially be set to success. At this step, the lower limit of the one-sided 97.5% confidence intervals (CI) will be calculated. Serial calculations will then be performed using a decreasing number (i.e., $n-1$, $n-2$, ...1) of successes to determine the maximum number of additional failures allowed for the lower bound one-sided 97.5% CI of the effectiveness endpoint percent estimate to achieve or exceed 75% success.

**Sensitivity Analysis of Objective #2:**

- **Tipping Point Analysis:** All discontinued primary eyes will be iteratively imputed as effectiveness success or failures. Let $n_1$ and $n_2$ be the number of discontinued primary eyes for the randomized surgery group and the randomized control group, respectively. For the $n_1$ discontinued randomized surgery group primary eyes, they can be imputed as 0 failures, 1 failure, 2 failures, and up to $n_1$ failures, for a total of $(n_1+1)$ possible imputations. For the $n_2$ discontinued randomized control group primary eyes, there are $(n_2+1)$ possible imputations. Therefore, there are $(n_1+1) \times (n_2+1)$ possible combinations of success and failure imputations for these discontinued
primary eyes. For each of these possible imputations, the lower limit of the one-sided 97.5% confidence intervals (CI) will be calculated. The imputations that have the lower one-sided 97.5% CI < 75% will be identified.

11.9 Analysis of Safety Data

Safety data such as BCDVA, slit lamp findings, and fundus findings will be summarized descriptively (mean, standard deviation, minimum, and maximum for continuous outcomes, and counts and percentages for categorical outcomes) for primary and all eyes.

For IOP at each visit, the mean, standard deviation, minimum and maximum and change from baseline will be summarized for all implanted eyes. Additionally, number and percentage of eyes with a IOP change from baseline of “decrease > 10 mmHg”, “decrease ≥ 5 mmHg to ≤ 10 mmHg”, “change within ± 4 mmHg”, “increase ≥ 5 mmHg to ≤ 10 mmHg”, and “increase > 10 mmHg” will be prepared for each study visits.

Manifest spherical equivalence (MRSE) will be summarized descriptively with the 95% confidence interval for the mean for primary eyes and all eyes at each visit. Additionally, the same analyses will be performed on the MRSE adjusted by normal aging (i.e., minus 0.082 D per year\(^\text{1,2,3,4}\)).

11.10 Analysis of Other Clinical Parameters

Means, standard deviations, and ranges will be derived from the continuous measurements; numbers and percentages will be used for summarizing the categorical outcomes. No specific claims will be made based on outcomes not pre-specified as an endpoint and no p-values will be presented for analyses without a pre-specified hypothesis.

---

\(^{1}\)Grosvenor T and Skeates PD. Is there a hyperopic shift in myopic eyes during the presbyopic years? Clin Exper Optom 1999;82:236-243

\(^{2}\)Charman WN. Developments in the correction of presbyopia I: spectacle and contact lenses. Ophthalmic Physiol Opt 2014;34:8–29


near visual function will be lost. Subjects will be encouraged to complete all questions and missing data will not be imputed. The PRO data will not be used to support specific labeling claims, thus this assessment is not a formal study endpoint. The PRO data will be described in the product labeling using descriptive statistics only. The difference between the baseline and 12 month NAVQ scores will be calculated for each participant to determine if there is a measurable improvement in subjective report of near visual function. Correlations between the change in near visual function (NAVQ score) and overall satisfaction (0=completely satisfied; 4= completely unsatisfied) and changes in objective measures of monocular and binocular DCNVA will be investigated using correlation coefficients in linear regression models. It is hypothesized that there would be a moderate positive correlation between DCNVA and NAVQ score based on previous associations found between this instrument and visual acuity.

The stability of any improvement in near visual function (NAVQ score) will be assessed by evaluating the change in scores across the post-operative follow-up visits (6, 12, 18 and 24 months) using Generalized Estimating Equations (GEE) models. Responses to the NAVQ questions will be used to develop an initial raw score based on the scale shown on the NAVQ. The NAVQ was developed using the Rasch model and is recommended to be scored using item response theory.[1]

As the NAVQ will be administered before and after surgery, all response data will be scored using the Andrich Rating Scale model for polytomous data in WinSteps (Version 3.80.1 Chicago, IL). Interval scores will be produced for each participant based on their responses to the 10-item NAVQ before surgery and at each follow-up visit and rescored onto a 0-100 scale for ease of interpretation. Rasch analysis weights the items and the scales for the responses to adjust for the varying level of difficulty for the tasks described in each item.

11.1 Additional Studies

For substudies, only observed data will be used for analysis and only descriptive statistics will be performed. All statistical analyses for substudies will be exploratory, since no formal secondary objective is specified in this statistical methods section.

---

12.0 STUDY MONITORING

Sponsor or CRO personnel will monitor all clinical studies in accordance with FDA guidelines. Study monitoring will involve the following elements:

- Sponsor or CRO personnel will meet with Investigators prior to the initiation of the study in order to review the adequacy of the facility, equipment and clinical personnel with respect to the needs of the study and to familiarize the Investigator and clinic staff with the protocol.

- Sponsor or CRO personnel will meet with Investigators and clinic staff at initiation of the time of study to ensure that subjects are being properly consented, the protocol examination methods are being complied with and that study data is being properly recorded.

- Sponsor or CRO personnel will meet with the Investigator and clinic staff at any time during the study regarding study conduct to ensure ongoing compliance with the protocol and data recording requirements.

- Sponsor or CRO personnel will maintain ongoing email and telephone communication with the Investigator and clinic staff regarding study conduct.

- The CRO shall select, train and manage qualified contract personnel to visit each Investigational site to review and monitor source documents and electronic data in accordance with FDA guidance.
13.0 REFERENCES


APPENDIX 1: EXAMINATION METHODS

Refractions and acuity measurements shall be obtained by an ophthalmologist, optometrist or trained technician (who is supervised directly by the ophthalmologist or optometrist).

**Manifest Refraction**

Manifest refraction will be performed pre and post-operatively using ETDRS acuity charts and standard phoropters. All systems will employ actual or equivalent optical distances of at least 4 meters (13 feet) and ambient lighting will be adjusted based on chart specifications. Chart luminance will fall within the ANSI required range of 80-160cd/m² and chart contrast will be a minimum of 85%.

**Cycloplegic Refraction**

Cycloplegic refraction will be performed ~ 20 minutes after application of 1 drop of tropicamide 1% at select pre and post-operative visits using the same systems as for manifest refraction.

**Instrument for Measuring Visual Acuities**

All visual acuities will be measured via the OPTEC 6500 (Stereo Optical, 8623 W. Bryn Mawr Ave., Suite 502, Chicago, IL 60631 USA 1.773.867.0380 or 1.800.344.9500). This system utilizes a lens system to simulate various test distances for distance, intermediate and near. The Optec 6500 has a microprocessor controlled internal illumination system that results in constant luminance of 85cd/m²; therefore, normal ambient lighting may be used as lighting conditions are not a factor in the testing set up. The manufacturer’s instructions for use will be provided to each Investigational site.

**Distance Visual Acuity**

Distance visual acuity will be measured at a simulated (optical) distance of 20 feet.

**Intermediate Visual Acuity**

Intermediate visual acuity will be measured at a simulated (optical) distance of 66cm.

**Near Visual Acuity**

Near visual acuity will be measured at a simulated (ocular) distance of 40cm.

**Determination of Near Add**

The add power will be determined by adding plus lenses, using the Optec 6500 at a simulated distance of 40cm.

**Determination of Dominant Eye**

The subject will be advised to perform the following steps for determination of the dominant eye.

1. Hold your hands at arm’s length out in front of you. Your palms should be pointing forward - in other words, you should be looking at the backs of your hands.
2. Make a “triangle.” Extend both of your thumbs so that they’re roughly perpendicular to the rest of the hand. Overlap your hands so that the space between makes a triangle. Your two
thumbs should be at the bottom of the triangle, while the edge and index finger of each hand form the two remaining sides.

3. The triangle space between your hands acts as a viewing window - you should be able to clearly see objects through it.

4. Look at an object through the triangle hole made by your hands with both eyes open. Find a nearby object that's small enough (or far enough away) that you can see the whole object through the viewing window between your hands. This can be anything - a door knob, a coffee mug, or even a letter on a faraway billboard.

5. Focus on the object. Try to focus your eyes on the object between your hands - not your hands themselves. Your hands should become somewhat blurry, while the object remains clear and in-focus. It's important to line this object up directly in front of you and to stare straight at it - turning your head to either side can distort your results.

6. For best results, at this point, make minor adjustments to your hands so that the object you're looking at fits almost exactly within the edges your viewing window. In other words, if your triangle is bigger than the object you're looking at, move your hands together to make it smaller, and vice versa.

7. Alternate closing each eye to see which gives better vision. Close one eye, then open it and close the other. Each time you switch eyes, the object you're looking at should do one of two things. It should either become obscured behind one of your hands or remain visible. Next, try your other eye. Your dominant eye is the one that allows you to see the object while it remains open.

**Scleral Thickness Measurement**

Scleral thickness will be measured and printed using the Sonomed Ultrasonic Biomicroscope (UBM). The manufacturer’s instructions for use will be provided to each Investigational site.

**Pupil size, shape and reaction**

The NeurOptics Pupillometer is a portable, battery-operated, hand-held device used to measure the iris’ reaction to a standardized level and duration of light. The manufacturer’s instructions for use will be provided to each Investigational site.

The pupils of both eyes will be assessed at each and every visit as follows:

- Round
- Elliptical
- Irregular
**Slit Lamp Evaluation – Grading**

**Lids / Lashes**

Blepharitis (using the Efron Grading scale and reference drawings):
- 0 = none
- 1 = trace (1+)
- 2 = mild (2+)
- 3 = moderate (3+)
- 4 = marked / severe (4)

**Meibomian Gland Dysfunction (using the Efron Grading scale and reference drawings):**
- 0 = none
- 1 = trace (1+)
- 2 = mild (2+)
- 3 = moderate (3+)
- 4 = marked / severe (4)

**Cornea**

Superficial punctate keratitis (using the Efron Grading scale and reference drawings):
- None
- Mild
- Moderate
- Marked or Severe

**Corneal abrasion:**
- None
- Tiny
- 1-2mm
- 2-3mm
- > 3mm

**Corneal edema (using the Efron Grading scale and reference drawings):**
- 0 = no evidence of corneal edema
- 1 = trace corneal edema (edema involves 0% to 5% of the cornea)
- 2 = mild corneal edema (edema involves 5% to 25% of the cornea)
- 3 = moderate corneal edema (edema involves 26% to 50% of the cornea)
- 4 = marked/severe corneal edema (edema involves > 50% of the cornea)

**Corneal endothelial gutatta:**
- 0 = no corneal gutatta
- 1 = rare corneal gutatta
- 2 = few corneal gutatta
- 3 = many corneal gutatta
- 4 = marked/severe corneal gutatta with stromal edema and bullous lesions
- Other abnormal corneal findings (specify)
Conjunctiva

Conjunctiva injection (using the Efron Grading scale and reference drawings):
  - 0 = none
  - 1 = trace (1+)
  - 2 = mild (2+)
  - 3 = moderate (3+)
  - 4 = marked/severe (4)

Subconjunctival hemorrhage:
  - 0 = none
  - 1 = less than or equal to 1 quadrant
  - 2 = 2 quadrants
  - 3 = 3-4 quadrants

Conjunctiva edema:
  - 0 = none
  - 1 = trace
  - 2 = mild
  - 3 = moderate
  - 4 = marked/severe

Other abnormal conjunctival findings (specify)

Crystalline Lens

Crystalline lens pathology using the LOCSII scale (with reference photos as published in Archives of Ophthalmology July 1989) as follows:
  - Normal
  - Lens Opacity
  - Other Abnormal Findings (specify)

If lens opacity, please complete the following:
  - Nuclear/Color Opalescence: □ N0 □ N1 □ N2 □ N3
  - Cortical: □ C0 □ C1 □ C2 □ C3 □ C4
  - Posterior Subcapsular: □ P0 □ P1 □ P2 □ P3
  - Anterior Subcapsular: □ A0 □ A1 □ A2 □ A3
**Anterior Chamber**

Cell and flare will be graded according to the SUN grading scheme (using a 1x1 mm slit lamp beam):

**SUN Grading for AC Cells**

<table>
<thead>
<tr>
<th>GRADE</th>
<th>CELLS IN 1x1mm Field</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;1</td>
</tr>
<tr>
<td>0.5+</td>
<td>1-5</td>
</tr>
<tr>
<td>1+</td>
<td>6-15</td>
</tr>
<tr>
<td>2+</td>
<td>16-25</td>
</tr>
<tr>
<td>3+</td>
<td>26-50</td>
</tr>
<tr>
<td>4+</td>
<td>50+</td>
</tr>
</tbody>
</table>

**SUN Grading for AC Flare**

<table>
<thead>
<tr>
<th>GRADE</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1+</td>
<td>Faint</td>
</tr>
<tr>
<td>2+</td>
<td>Moderate (iris/lens details clear)</td>
</tr>
<tr>
<td>3+</td>
<td>Marked (iris/lens details hazy)</td>
</tr>
<tr>
<td>4+</td>
<td>Intense (fibrin/plastic aqueous)</td>
</tr>
</tbody>
</table>

**Iris appearance**

- 1 = Normal
- 2 = Abnormal (if abnormal, please describe)
**Intraocular Pressure**

Intraocular pressure will be measured using Goldmann applanation tonometry. Measurements will be taken according to the published guidelines set forth by Michael A. Kass [Kass MA. Standardizing the measurement of intraocular pressure for clinical research. Guidelines from the Eye Care Technology Forum. Ophthalmology. 1996 Jan;103 (1):183-5]. Copies of this guideline will be provided to all sites.

**Gonioscopy**

The angle will be evaluated using a 3 or 4 mirror lens and the following grading scheme:

- Grade 3 – 4 (Wide Open: Angle > 20 degrees < 45 degrees)
- Grade 2 (Moderately Narrow: Angle = 20 degrees)
- Grade 1 (Extremely narrow: Angle = 10 degrees)
- Grade 0 (Angles Closure: Angle + 0 degrees)
- Other: (Specify)

**A-Scan**

Axial length and ACD will be measured and recorded.

**Internal Examination**

**Peripheral Fundus Examination**

- Normal
- Abnormal (if abnormal, please describe)

**Cup to Disc Ratio** will be assessed by means of a dilated fundus exam using condensing lenses and the slit lamp biomicroscope.

**Other Observations:**

Photographs, drawings and / or standard descriptive ophthalmic terms may be used as needed to describe any other ocular findings.
1. Refraction (sphere and cylinder) over a calculated 4 mm entry pupil,
2. Zernike polynomials up to the eighth order,
3. RMS of higher order aberrations (HOA)
4. Total depth of focus (DoF).

Defocus Curves

Defocus curve testing will be performed to subjectively measure the effectiveness of presbyopia correction by using minus and plus lenses. Testing will be performed using phoropter with a computer-controlled LCD distance chart with ETDRS letters at 6m/20ft. The phoropter will contain the subject's best manifest distance refraction.

A range of lens powers from -4.00 D to +2.00 D will be used over the best distance refraction for this testing. The lens power in the phoropter will be progressively reduced in +0.50 D steps, starting at -4.00 D and moving towards +2.00 D. After each lens power change, the letters should be changed to a new set of letters of the same size or smaller and the letters read per line should be recorded. The testing should proceed as follows:

1. The subject should be seated and looking through a phoropter with the contralateral eye occluded.
2. The computer-controlled ETDRS letter chart should be used at a 6 m/20ft distance from the patient.
3. The patient's best distance correction should be dialed in to the phoropter.
4. With the patient viewing the smallest letters corresponding to the patient's BCDVA, a -4.00D lens should be added to the patient's distance correction. (If the subject cannot read any of the letters, the letter size should be increased by 1 line until the acuity can be measured.) As the letters are read, the correct letters should be circled and the visual acuity should be recorded with the corresponding lens power. To prevent memorization, the letters should be changed to a new set of letters between each lens change and reading attempt.

**If the patient reads all the letters on the line correctly, then switch to the next smallest line of letters and instruct that patient "Can you read any letters on this next smallest line?" If the patient again reads all letters correctly, repeat until either some or all letters in the next smallest line are missed. Once the subject has missed letters, do not proceed to the next line and only record the letters that the subject got correct. (If 5 letters on the line are read plus 2 letters on the next line down, the total is 7 letters). In addition, record the corresponding acuity for the previous line, where all the letters were read correctly.**
Repeat the testing sequence on the fellow eye with the other eye occluded.

The above defocus testing protocol is based on the following publication with associated graphs:

APPENDIX 2: VISABILITY IMPLANT SYSTEM SURGICAL PROCEDURE

The VisAbility Implant System surgical procedure is performed as an outpatient procedure by the Investigator as described and categorized in eight major steps below.

1. Marking

Approximately ten minutes prior to the procedure, a topical anesthetic such as proparacaine ophthalmic solution or equivalent is instilled in the eye(s). With the patient in the standing or seated position and fixating on an object straight ahead, mark the limbus at 12:00 and 6:00 o'clock with a sterile gentian violet marker. Reinforce these marks as needed and place on drop of Brimonidine 0.1% or 0.15% or equivalent on the patient's operative eye. Have the patient close their eyes for two minutes.

In the operating room, with the patient's vital signs monitored, use systemic relaxation as needed (e.g. Valium, Fentanyl, and/or Versed). Clean the eye and the skin around the eye in the usual manner for sterile intraocular surgery and drape the patient and their lids and lashes from the surgical field. Use a locking eyelid speculum that will hold the eyelids widely open. Instill sterile 2% xylocaine drops without epinephrine or equivalent topically to the cornea and conjunctiva, drying off any excess.

Positively identify the superior and inferior rectus muscle insertions and the anterior ciliary arteries accompanying them such as by gently blanching the area with a flat spatula or the flat handle of a forceps or other alternative method. Confirm that the previously placed 6:00 and 12:00 o'clock limbal marks correspond to the axis of the center of the respective rectus muscle insertion or correct their position to this axis as needed.

On a relatively dry limbus, align the positioning barrel to the geometric limbus and rotate it to align the internal grooves with previously placed limbal marks. Place the barrel marker in its positioning slits and mark the eye.

2. Peritomy

Re-institute sterile 2% xylocaine drops without epinephrine or equivalent topically to maintain good anesthesia.

Make two 3 mm or longer vertical conjunctival incisions approximately 0.5mm from the limbus at 3 and 9 o'clock using a 0.3 forceps and blunt Westcott scissors. Taking care not to tear the conjunctive, utilize blunt Westcott scissors to bluntly dissect posteriorly into sub-Tenon's space at an angle to avoid the horizontal plane of the medial and lateral recti muscles.

1
With a blunt cannula on a syringe containing sterile 2% xylocaine solution without epinephrine or equivalent, enter the sub-Tenon’s space posteriorly. Advance the cannula and then sweep the cannula toward the limbus. Inject about 0.25 cc of the sterile 2% xylocaine solution without epinephrine or equivalent in each of the 4 quadrants.

After the sub-Tenon’s injection of anesthetic has been completed, perform a 360 degree limbal peritomy of the conjunctiva and Tenon’s capsule.

Upon completion of the peritomy inspect the sclera at 3, 6, 9 and 12 o’clock for bare sclera in preparation for placement of the VIS Docking Station. Utilize an absorbent stick, forceps if additional blunt dissection of the sclera is required.

**CAUTION:** If after completing the conjunctival peritomy, the surgeon observes the insertions of the rectus muscles nearer than 4.5mm posterior to the limbus, aborting the procedure and closing the conjunctiva must be considered. This is done to avoid the risk of impinging upon the vasculature supplying the anterior segment, thus decreasing the risk of Anterior Segment Ischemia.

**CAUTION:** Due to the potential of a detrimental effect on perfusion and/or scleral thickness, bipolar and/or thermal cautery should not be used during surgery.

### 3. VIS Docking Station Placement

Place the VIS Docking Station on the eye by holding the unit slightly above the eye. Carefully drape the conjunctiva over the four corners and perimeter of the VIS Docking Station to avoid engaging any conjunctiva in the helical twists.

Center the VIS Docking Station on the geometric limbus by keeping the inside diameter of the unit concentric with the limbus. Maintain the desired rotational position by aligning the 6 and 12 o’clock internal arrow points on the unit with the 6 and 12 o’clock limbal marks and the docking channels on the unit with the oblique line marks from the VIS Barrel Marker.

Once concentricity and rotational position have been satisfactorily achieved, use the VIS Actuation Tool to rotate each of the four fixation points clockwise 180˚ to the stop while pressing down on the VIS Docking Station to engage the helical twists into the limbal sclera.

After fixation, visually confirm satisfactory x/y and rotational positioning and verify sufficient four-point fixation of the VIS Docking Station by lightly proptosing the eye with gently lifting of the unit. Reposition if necessary.
4. Lamellar Scleral Tunnel Creation

Each of four tunnels will be created solely with the VIS Scleratome positioned by the VIS Docking Station.

Use of a manual lamellar blade is not allowed for use in creating or augmenting any scleral tunnel.

Tunnels should be created in the following sequence to facilitate hand positioning and ensure the superior temporal quadrant tunnel is created last, due to the sclera in that quadrant being the thinnest on the eye:

1. Inferior Nasal (IN)
2. Superior Nasal (SN)
3. Inferior Temporal (IT)
4. Superior Temporal (ST)

Beginning with the inferior nasal quadrant, rotate and proptose the eye to provide adequate exposure of the sclera. Confirm the sclera near the VIS Docking Station is bare. Perform additional blunt dissection if required.

Prior to placing the VIS Scleratome, verify the winding knob has been fully actuated.

Dock the VIS Scleratome locating ridge to the corresponding channel in the VIS Docking Station and line up the blade guard with the surrounding edge. While maintaining this docked position, bring the VIS Scleratome perpendicular to the sclera such that the footplate is flat to bare sclera.

With a balance of pressure with the VIS Scleratome and proptosis with the VIS Docking Station, activate the VIS Scleratome by advancing the slide button toward the eye.

Confirm the length of each lamellar scleral tunnel created using the VIS Spatula.

Caution: When advancing the VIS Spatula thru the scleral tunnel, the leading tip must be directed outwards (anteriorly) along the roof of the tunnel to facilitate exiting from the tunnel and to avoid unintentional scleral perforation.

To minimize manipulation of the eye, a VIS Implant Segment should be placed in each Lamellar Scleral Tunnel made prior to proceeding to the creation of the next Lamellar Scleral tunnel. If for any reason, only one or two Lamellar Scleral Tunnels are able to be implanted with VIS Implant Segments, these segments will be removed from the eye.

The VIS Scleratome requires winding of the knob prior to creation of the next scleral tunnel.
Implantation of the VisAbility Implant Segment

To facilitate hand positioning, inferior quadrant tunnels (IN and IT) should be entered forehand from the inferior end of the tunnel. Superior quadrant tunnels (SN and ST) should be entered backhand from the superior end of the tunnel.

While continuing to maintain fixation of the eye with the VIS Docking Station, immediately after the creation and verification of each tunnel, grasp the Shuttle / Implant segment assembly approximately 12mm from its leading edge and insert the front end of the shuttle into the tunnel and advance the VIS Shuttle / Implant segment assembly into the tunnel.

**CAUTION:** When advancing the VIS Shuttle / Implant segment assembly thru the scleral tunnel, the leading tip must be directed outwards (anteriorly) along the roof of the tunnel to facilitate exiting from the tunnel and to avoid unintentional scleral perforation.

After 3mm or more of the VIS feeder tube has exited the tunnel, grasp the exited VIS feeder tube and pull the assembly until the feet of the VIS implant segment have exited the tunnel.

**CAUTION:** While pulling the VIS feeder tube thru the scleral tunnel, pay close attention that the Feeder tube does not begin to disinsert from the VIS implant segment prematurely.

After the feet of the VIS implant segment have exited the tunnel, continued pulling of the VIS feeder tubing will disinsert it from the VIS Main Body Implant allowing the compressed feet to open, effectively locking the VIS Main Body Implant into the tunnel.

Using the VIS Center insert implant loading forceps, grasp the top edges of the VIS Center Insert implant at the midpoint and guide it into the receiving slot of the VIS Main Body Implant. Use the VIS Center Insert implant loading forceps to then clasp the VIS center insert implant fully into the VIS main body Implant. A snap-like action will be apparent when the VIS center insert implant has been properly placed, in addition, the outer edge of the assembled VIS Implant Segment will line up flush and smooth.

Repeat tunnel creation and implantation for each of the four quadrants. If for any reason, only one or two Lamellar Scleral Tunnels are able to be implanted with VIS Implant Segments, these segments will be removed from the eye.
6. VIS Docking Station Removal

Use the Actuation Tool to rotate each of the four fixation points of the VIS Docking Station counterclockwise 180˚ to the stop, to disengage the helical twists from the limbal sclera and completely unlock the device from the eye. Once free of fixation, carefully lift the VIS Docking Station from the eye to avoid causing any corneal abrasion with the underside helical twists.

After lifting the unit from the eye, rinse away any excess clotted blood in the field. Reapply sterile 2% xylocaine drops without epinephrine or equivalent topically to maintain good anesthesia as needed. Check the implant location by measuring from the anterior center of the implant to the limbus.

7. Conjunctival Closure

Ensure adequate hemostasis is obtained prior to closing the conjunctiva. CAUTION: Due to the potential of a detrimental effect on perfusion and/or scleral thickness, bipolar and/or thermal cautery should not be used during surgery. Should hemostasis be required, Evicel fibrin sealant (Omrix Biopharmaceuticals, Ltd., Kiryat Ono, Israel) or TISSEEL fibrin sealant (Baxter International, Inc., Deerfield, IL) may be used. Bring the conjunctiva into position to approximate where it will need to be located when closed. Starting nasally, use a 9-0 braided Vicryl suture or equivalent with a modified matress technique, starting nasally, close 3 and 9 o'clock as needed such as using a 3mm scleral bite tangential to the limbus and a 4-5mm conjunctival bite then at 6 and 12 o'clock as needed. Care must be taken to ensure a smooth, uniform, minimally wrinkled conjunctival closure.

8. After Conjunctival Closure

At the completion of the surgery, a removable punctual plug should be placed in the inferior punctum and an initial dose of antibiotic drops such as moxifloxacin ophthalmic solution or equivalent and steroid drops such as prednisolone acetate 1% ophthalmic suspension or equivalent should be instilled in the eye. Instruct the patient to keep their eyes closed, and use ice compresses to decrease swelling.
Following surgery, physicians should adhere to the following guidelines of topical ophthalmic medications and care:

• To help control pain postoperatively, an icepack should be applied to the eye at intervals for approximately 30 minutes or longer as needed. A topical non-steroidal anti-inflammatory drug (NSAID) such as nepafenac ophthalmic suspension or equivalent may also be instilled immediately postoperatively. Chilled BSS may be instilled every 15 minutes and topical steroid drops such as prednisolone acetate 1% ophthalmic suspension or equivalent may be used every 15 to 30 minutes until the pupil reaction is greater than 25% as described in the next step. Prior to discharge the patient should be given Diamox 500mg Sequel PO or equivalent.

• Pupil functionality will be evaluated postoperatively using a NeurOptics Pupillometer every 15 to 30 minutes until the percent pupil constriction reading is at least 25%. A second, confirmatory reading of 25% or greater may be taken as soon as 5 minutes after the first. If two pupil constriction readings of at least 25% are not achieved within the first 4 hours after surgery, preparation for removal of the implant segments will commence. The Investigator must remove all four implant segments no later than 6 hours after the implantation surgery if the two pupil constriction readings of at least 25% are not achieved within 6 hours postoperatively.

• During the first week after the surgery, antibiotic drops such as moxifloxacin ophthalmic solution or equivalent and topical steroid drops such as Lotemax gel or equivalent should be instilled in the eye. Additionally, NSAIDs such as topical nepafenac ophthalmic suspension or equivalent and / or oral medications such as naproxen or equivalent or acetaminophen with codeine or equivalent may be given as needed for pain during this time.

Procedure to Surgically Remove VIS Implant Segments

Subjects may request to have the VIS implant segments removed at any time. The VIS Implant segment removal procedure, if requested and deemed safe to do so by the Investigator will be performed by the Investigator as described below.

Magnification of the surgical area at a surgical microscope is advised. Preoperative sterile prep and drape is required. Topical anesthesia with sterile 2% xylocaine drops without epinephrine or equivalent should be applied to the operative eye requiring implant segment removal. A drop of Brimonidine 0.1% or 0.15% or equivalent may also be used to decrease bleeding. Using a sterile sharp blade such as a 15 degree ophthalmic sharp, 18 to 21 gauge hollow injection needle, or equivalent, a small (2mm) scratch incision of the conjunctiva is made over both exposed ends of the VIS Implant segment. Use a forceps such as a .12 forceps to further expose the ends of the VIS Implant Segment from the overlying conjunctiva.
Once the ends of the VIS Implant segment are unencapsulated, grip the solid end of the VIS Main Body implant with the jaws of the VIS Cutter (966-0030) with the tips perpendicular to the length of the implant and one tip flat to the sclera. Ensure that the full portion of the widened extralamellar scleral tunnel portion of the VIS Main Body implant is fully enclosed within the VIS Cutter. Close the VIS cutter to sever the complete solid, wide end of the VIS Main Body Implant.

Carefully remove the severed piece(s) of the VIS Main Body implant from the Cutter and inspect the cut end for any barb that might remain and carefully sever it.

Using the VIS Implant Loading Forceps, the distal end of the Shuttle forceps or other toothed forceps grasp the uncut end of the VIS Implant segment, and pull it through the tunnel with a slight twisting motion to remove it from the eye.

Repeat for each Implant segment requiring removal.

After completing removal of all required VIS implant segments, the scleral and conjunctival areas that have been opened should be assessed to see if they will heal primarily, if they need inflated with an intracanal injection of BSS or need to be sutured with an appropriate gauge suture.

An initial dose of antibiotic drops such as moxifloxacin ophthalmic solution or equivalent and steroid drops such as prednisolone acetate 1% ophthalmic suspension or equivalent should be instilled in the eye.

A light dressing may be applied to keep the eyes closed over night for patient comfort.

During the first week after the surgery, antibiotic drops such as moxifloxacin ophthalmic solution or equivalent and topical steroid drops such as prednisolone acetate 1% ophthalmic suspension or equivalent should be instilled in the eye. Additionally, NSAIDs such as topical nepafenac ophthalmic suspension or equivalent and/or oral naproxen or equivalent may be given as needed for pain during this time.
APPENDIX 3: PATIENT-REPORTED OUTCOME (PRO) INSTRUMENT FOR USE IN PROTOCOL VIS-2014

I. Introduction

The Near Activity Visual Questionnaire (NAVQ) is a PRO instrument designed for use in study subjects receiving presbyopia correcting devices and is currently being used in an ongoing IDE study. The Near Activity Visual Questionnaire (NAVQ) consists of 10 items which are combined to produce a single score for near visual function and an 11th item which is a global satisfaction question.

In Protocol VIS-2014 the NAVQ will be administered at the pre-operative visit and at 6, 12, 18 and 24 months. The repeated assessments over the post-operative period will provide an indication of the stability of the near visual function. This schedule is appropriate for the purpose of assessing near vision before surgery and at a minimum of 6 months after surgery since it allows for recovery and adaptation to the bilateral surgery. The full questionnaire to be used in the IDE study of the VisAbility Implant System is provided in Exhibit A.

The NAVQ is uni-dimensional and produces a single score related to difficulty with near vision tasks. The global satisfaction question will be considered on its own and is not scored with the first 10 items.

II. Instructions for NAVQ Use

The NAVQ instrument should be self-administered to avoid bias in reporting, as recommended by the authors of the NAVQ.

It is anticipated that completion of the NAVQ will be a modest burden on the trial subjects. The layout and font size were optimized by the instrument developers for good legibility and self-administration, and it is being used as published.

At designated visits, the questionnaire will be completed by each study subject in the clinic, prior to any clinical assessments of vision. Study subjects will be instructed to answer each question about their recent everyday experience with near vision without any spectacle correction. All responses will be documented by the study subjects on a paper case report form. Subjects will be encouraged to complete the full questionnaire and completed questionnaires will be checked by clinic staff to ensure all questions were answered. The script to be used by clinic staff in instructing subjects on how to complete the PRO instrument is provided in Exhibit C.

It is critical that study subjects understand that they are reporting on their near visual function without the use of reading glasses. It is expected that study participants will be close to emmetropic with a need for some add power for certain near tasks. As a result, subjects will be instructed to answer the questions about their near vision when they are not using their reading glasses or any other corrective lenses.

Testing of the NAVQ has been associated with minimal missing data, indicating that the content of the questions is generally relevant and acceptable to patients who have had surgical correction of presbyopia.

[1, 3]
III. The PRO Instrument's Conceptual Framework

The sections below describe the NAVQ and its validation using the principles described in FDA's Guidance, "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims".

The NAVQ was designed with the stated purpose of creating a standardized questionnaire to subjectively assess near visual function and satisfaction with a variety of presbyopia-correction techniques.\[1, 2\] The NAVQ is a 10-item questionnaire with an additional global question about satisfaction. The 10-items are combined into a single score where high scores indicate greater difficulty with near vision tasks (Table 1). The NAVQ therefore measures the construct of difficulty with near visual tasks using 10 items and the concept of 'satisfaction with near vision' is assessed separately with a single global question (Figure 1).

IV. Content Validity Documentation

A. Literature review and documentation of expert input:
The patient perspective on the outcome of a medical intervention is helpful because such a perspective may provide supplemental information both to patients and physicians regarding the performance of the intervention. The VisAbility Implant Procedure is designed to improve near vision in presbyopic patients. The primary outcome of the proposed trial is the improvement in distance corrected near visual acuity (DCNVA) at a distance of 40cm in the primary eye at 12 months. However, the VisAbility Implant Procedure is a bilateral procedure and the NAVQ may provide additional patient perspective on reduction in limitations in vision due to presbyopia.
A review of the literature has been completed to identify a suitable PRO instrument. Cochener published a meta-analysis of outcome data for clinical trials of multifocal intraocular lenses in 2011 which included literature up until June 2009. Like the VisAbility Implant System, multifocal IOLs are designed to correct presbyopia. While there was uniformity in the collection of visual acuity data, there was no consistency in the questionnaires used for Patient Reported Outcomes (PRO). Patient satisfaction and spectacle independence have mostly been collected as individual items, usually on a Likert scale (14/20 trials). One trial used the VF14 index, a questionnaire designed to assess the impact of cataract on visual function.

Although there are a number of PRO questionnaires related to visual function that have undergone extensive validation, only one was specifically conceptualized, designed and validated for the assessment of the correction or reduction of presbyopia. That questionnaire is the Near Activity Visual Questionnaire (NAVQ).

B. Qualitative study protocols

The NAVQ was developed with the aim to be able to assess near visual function and satisfaction with a variety of presbyopia-correction techniques. As the VisAbility Implant Procedure is a surgical correction for presbyopia, the application of the NAVQ falls within the scope of the intended population for this instrument. Because NAVQ is a published instrument for which content validity has already been demonstrated as described herein, Refocus Group, Inc. has not performed additional qualitative studies to investigate content validity.

C. Origin and derivation of items with chronology of events for item generation, modification and finalization:

The development of the NAVQ has been described in a publication by Gupta, et al (n=22) and in a second larger study by Buckhurst, et al (n=150). The processes of item generation involved a review of published vision-related quality of life (VR-QOL) questionnaires to identify any items relating to near vision tasks. This search found 374 candidate items. This bank of items was reduced by combining duplicate items and through review by ophthalmic professionals (5 ophthalmologists and 3 optometrists) and 10 laypeople with presbyopia at which time it was possible to add questions to cover any new areas identified. This review process resulted in 19 candidate items which was reduced to a 9-item questionnaire plus a global question about satisfaction using the Rasch Model. Though this questionnaire was considered to be internally consistent, reliable and a valid instrument for assessing accommodating IOLs, the authors suggested the addition of items to better target patients with good near vision and to allow assessment of other types of presbyopic correction. Subsequently, Buckhurst expanded the instrument to 26 items and revisited the psychometric properties in a population of 150 patients with varying types of corrections for presbyopia.
The Rasch model was used to reduce the 26 items to those relevant to near visual function, the concept being measured.\[1\] The number of items was reduced by considering in priority order: item fit statistics, item targeting, frequency of endorsement and skew and kurtosis. The outfit mean square was required to fall within the range of 0.6 to 1.4 where items below 0.6 were considered too predictable and those above 1.4 were considered too variable. The targeting was evaluated using a person map of items.\[4\] Frequency of endorsement was kept in the range of 65 to 85% to ensure the questions were relevant. Skew indicates the symmetry of the frequency distribution of responses and kurtosis the height of the peak of the distribution. Items with skew or kurtosis >2 were excluded. Items were removed one at a time and item statistics recalculated each time until all of the items fitted the Rasch model.\[1\] This final NAVQ had 10 items and a global item about satisfaction.

D. Summary that supports content validity:

**Item content:** The involvement of patients in review of the candidate items is recommended in the FDA guidance document regarding the use of PRO's in clinical studies.\[5\] Patient input was part of the development of the NAVQ instrument as described above.\[2\] Additionally, Refocus Group, Inc. has conducted a pilot study to confirm whether patients who have undergone the VisAbility Implant Procedure understand the NAVQ and are able to answer the questions. The NAVQ was administered over the telephone to 11 post-operative subjects in the IDE G970152 clinical trial so their understanding could be ascertained. The subjects were able to understand and answer all of the questions.

**Response Options:** During development, items were required to have frequency of endorsement in the range of 65 to 85% to ensure the questions were relevant but not redundantly predictable.\[1\] All items were originally assigned a 6-point Likert scale, however the rating scale was scrutinized using category function statistics to refine the response scale and a 4-point scale was recommended.\[1\] With the 4-point scale, respondents were able to use the scale to reliably represent their level of difficulty with the task. For the satisfaction scale the 6-point Likert scale was retained. All items are consistent in that higher scores represent greater difficulty or greater dissatisfaction.

**Recall period:** The questionnaire does not specify a recall period and refers to the patient's current vision status. As the tasks are commonly encountered in everyday life, the subject should be able to reference a recent experience within the past few days relevant to all questions in the NAVQ. If a subject does not perform an activity or has stopped doing the activity for a reason other than because of their vision, they will be asked to answer "0", for "Not Applicable". As the instrument is scored using the Rasch model rather than a raw score, the person score can be created despite any missing data for individual items.

**Scoring:** The instrument is recommended to be scored using the Rasch Model to enable generation of an interval score.\[1\] Buckhurst validated the scoring in a clinical population comprised of 150 subjects including patients with a range of corrections for presbyopia: monofocal, accommodating, and multifocal intraocular lenses, multifocal contact lenses and varifocal spectacles. The questionnaires were administered 3 months after any surgeries, 1 month after contact lens fitting and 3 to 8 months after varifocal spectacles were dispensed.
Table 1 summarizes the patient characteristics in the validation study and Table 2 shows the NAVQ scores stratified by type of correction. In the table, a lower score represents better near visual function.

### Table 1: Characteristics of Patients Recruited for Validation of NAVQ

<table>
<thead>
<tr>
<th>Type of Correction</th>
<th>N=20 (13%)</th>
<th>N=60 (40%)</th>
<th>N=30 (20%)</th>
<th>N=20 (13%)</th>
<th>N=20 (13%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monofocal IOL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multifocal IOL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accommodating IOL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multifocal spectacles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varifocal spectacles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Age, mean±standard deviation [range]:
- 63 years±11 [30-82]

Sex, male:female:
- N=66:n=84

### Table 2: NAVQ Scores Rescaled to 1-100 for Each Type of Presbyopia Correction

<table>
<thead>
<tr>
<th>Type of correction</th>
<th>Mean NAVQ score ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monofocal IOL</td>
<td>59.0 ± 10.5</td>
</tr>
<tr>
<td>Multifocal IOL</td>
<td>18.9 ± 13.2</td>
</tr>
<tr>
<td>Accommodating IOL</td>
<td>34.2 ± 12.1</td>
</tr>
<tr>
<td>Multifocal spectacles</td>
<td>24.0 ± 11.6</td>
</tr>
<tr>
<td>Varifocal spectacles</td>
<td>17.9 ± 11.6</td>
</tr>
</tbody>
</table>

V. Assessment of Other Measurement Properties

The attributes of reliability, validity and ability to detect change have been assessed during instrument development and these reports have been published. and are summarized as follows.

A. Reliability:

It is important that a PRO can yield a consistent, reproducible estimate of effect. The repeatability of the NAVQ score has been assessed by calculating its intra-class correlation coefficient (ICC) in a subset of 90 patients who repeated the NAVQ two weeks after the first administration. The 2 way random effects intraclass correlation coefficient (ICC) for test-retest reliability was estimated as 0.72. This can be interpreted as high reliability. Internal consistency was also investigated and the Cronbach α coefficient was 0.945 showing good construct validity. The instructions for completing the questionnaire will be scripted to ensure no variability between administrations such that the reliability of the instrument will be maintained during the IDE study.
B. Construct validity:

Buckhurst investigated the relationship between the NAVQ and objectively measured distance corrected near visual acuity (DCNVA, logMAR) and critical print size (CPS). CPS was the smallest print size on the Minnesota Low Vision Reading Test (MN-Read) chart that could be read at the patient's maximum reading speed. The correlation coefficient was 0.543 for DCNVA and 0.526 for CPS representing moderate correlations.

The moderate correlation to reading is not surprising, since reading speed can also be affected by motivation, education and intelligence; and DCNVA at a standardized distance by no means captures the variability in near tasks and preferred working distances among patients.

C. Ability to detect change:

The person separation index (PSI) is the ratio of the true variance in the estimated measures to the observed variance and indicates the number of distinct person strata that can be distinguished by the PRO. The NAVQ was reported to have a PSI of 2.92 which indicates excellent discriminant ability. Further, the NAVQ demonstrated the ability to distinguish between different types of presbyopia correction. It is anticipated that the NAVQ will be able to measure a change in near visual function from before to after surgery and determine if the near visual function is relatively stable across visits.

VI. Interpretation of scores

The NAVQ provides a score for patient reported near visual function and satisfaction with presbyopia correction. It was found to be reliable and valid, using standard, current psychometric techniques. The NAVQ was also able to discriminate between those with and without near vision difficulties as shown by the difference in mean scores by type of refractive correction (Table 3) and as shown by the separation index (2.92). Therefore, NAVQ interval scores provide a relative measure of difficulty with near visual tasks and can be compared between subjects and across different time points.

VII. Language and cultural adaptation

The NAVQ was developed and validated in the United Kingdom in an English speaking population. The questionnaire has been pilot tested with 11 patients who have undergone the VisAbility Implant Procedure. All questions were understood and there was no missing data. Because the instrument has been successfully self-administered to 150 patients in the UK during development and in an evaluation of 15 patients in the UK with a diffractive trifocal IOL, it is likely that the readability is sufficient for an English speaking U.S. study population. As a result, the instrument will be administered in its original form in English without cultural adaptation.

VIII. Modifications

A comparison of the original NAVQ instrument provided in Exhibit B and the PRO instrument to be used in the IDE clinical study, Exhibit A, shows that they are virtually identical. The instructions, which have been adapted for the context of this trial, are also virtually the same as the original NAVQ instrument. Since there is only one presbyopic correction being considered, the field where type of presbyopic correction is indicated has been replaced with a single option. A subject identity field has been added at the top for completion by the clinical staff to ensure proper recordkeeping.
IX. Conclusion

Although the PRO outcomes are not intended to support specific labeling claims, the NAVQ questionnaire's characteristics, conceptual framework, content validity, and other measurement properties (i.e. reliability, construct validity, and ability to detect change) are adequate for the instrument to serve as an additional evaluation in the IDE investigation of the VisAbility Implant System.

X. Key references


The Sponsor shall provide training regarding the administration of the NAVQ questionnaire used in the clinical trial of the VisAbility Implant System. This administrative manual is the training to be used by the staff at the clinical sites.

This guidance includes instructions on WHEN the NAVQ is to be administered, WHERE the administration should take place, HOW it is to be given to the subject, HOW questions are to be answered and WHAT the plan is for the scoring process.

Clinic staff is to use the script provided in Section C below each time a subject is asked to complete the NAVQ questionnaire.

A. WHEN and WHERE to give the NAVQ:

The NAVQ should be given either in the waiting room or in the examination room BEFORE the patient has any examination of their vision by the doctor or study staff. It is not necessary for the subject to be in complete privacy while taking the short questionnaire, but study staff will be instructed to insure the subject completes the questionnaire independently.

B. HOW to give the NAVQ and HOW to answer questions:

1. Give the subject a pen and the paper copy of the NAVQ on a clipboard.

2. It is important that the patient is instructed to answer about their experience when not wearing reading glasses, magnifiers or corrective lenses of any type. Ask the subject if they understand what is meant by “reading glasses, magnifiers or corrective lenses.”

3. Verbally give the subject the scripted instructions, visually checking after each instruction to see if the subject apparently understood the instruction.

4. If subjects have questions, emphasize that there is no right or wrong answer and if they no longer perform some tasks due to non-visual reasons that they should mark “X” in the first column. If they have stopped doing a task because of vision, they should mark “3” for Extreme Difficulty.

C. Script for Administration of NAVQ:

1. ‘Please fill out this short questionnaire before we get started with the examination. You will need to write in your name, date of birth and today’s date. Circle the answer that most closely reflects your amount of difficulty with near vision tasks. There is no right or wrong answer. I will check that you have completed all questions but will not pay attention to any answers.’
2. 'You should answer the questions about your near vision when you are not wearing reading glasses or using magnifiers or corrective lenses of any type. Please let me know that you understand.'

3. 'The questions are about different activities where you need to see up close. Again, you should respond based on your experience with these activities when you are not wearing reading glasses.'

4. 'If you don’t do or have stopped doing the activity for a reason other than because of your vision – please circle ‘X’ in the first column for ‘not applicable.’ We would like you to complete all of the questions.'

5. 'Please answer the questions by writing on the paper form. Please answer the questions independently without advice or input of clinic staff or family members.'

Clinic staff is to check to determine that all questions have been answered and to ask the subject to complete any unanswered questions. Make sure that all fields are completed and that the Subject ID# is correct. Place the completed form without scoring in the subject’s study file.

WHAT the plan is for the scoring process. Scoring of the questionnaire results will not be conducted at the clinical sites. The Sponsor will handle the statistical scoring process for each NAVQ questionnaire at a later time.
APPENDIX 5: DATA SAFETY MONITORING BOARD CHARTER

Refocus Group, Inc.

DATA SAFETY MONITORING BOARD (DSMB) CHARTER

A PROSPECTIVE, MULTICENTER CLINICAL TRIAL OF
THE VISABIITY IMPLANT SYSTEM (VIS)
FOR THE IMPROVEMENT OF NEAR VISUAL ACUITY IN PRESBYOPIC
PATIENTS

Protocol: VSI-2014

Date of Protocol: October 13, 2014
Date of Protocol Amendment 1: January 10, 2015
1. INTRODUCTION

This charter governs the Data Safety Monitoring Board (the “DSMB”) established by Refocus Group, Inc. (the “Sponsor”) for the prospective, multicenter clinical trial of the VisAbility Implant System for the improvement of near visual acuity in Presbyopic patients under Protocol VIS-2014 (the “Clinical Trial”). The charter describes; the role and responsibilities of the DSMB, its members, conduct of meetings, its access to data and the manner of communication with the Sponsor.

2. ROLE OF THE DSMB: RESPONSIBILITIES & FUNCTION

The primary role of the DSMB will be to ensure subject safety during the conduct of the Clinical Trial.

The DSMB will periodically evaluate the conduct of the Clinical Trial, adverse events and related safety data, and efficacy data from the perspective of relative benefit. The DSMB will make recommendations to the Sponsor as follows.

The recommendations of the DSMB to the Sponsor may include:

Modification of the study protocol, subject to approval of FDA or the IRB as applicable.

Continuation of the study according to the protocol and any related amendments.

Modification of the manner of study conduct.

Discontinuation of the study (with provisions for orderly discontinuation in accord with good medical practice).

Discontinuation of enrollment into the study.

3. DSMB MEMBERSHIP

3.1 Members

The DSMB will consist of three members with at least two members being licensed ophthalmologists or optometrists. The names and contact information of the DSMB members are as shown in the Appendix and will be updated periodically as needed should changes in DSMB membership occur. A copy of each DSMB member's curriculum vitae, updated at least annually, will be maintained by the Sponsor and available upon request. DSMB members will not act as investigators or sub-investigators for the Clinical Trial and will have no involvement in the Clinical Trial outside their role on the DSMB. DSMB members may not participate in any other IDE clinical study of a presbyopia correcting surgical device or technique, other than studies of presbyopia correcting intraocular lenses, nor may DSMB members serve as a personal physician to any subject enrolled in the Clinical Trial.
3.2 Financial Disclosure and Conflict of Interest

Each DSMB member must disclose any financial or other material interests which may create a potential conflict with respect to their role on the DSMB including, but not limited to, equity interests in the Sponsor. Members of the DSMB will be responsible for advising the Sponsor of any change in related financial interests.

The Sponsor will be responsible for deciding whether financial or material interests may impact a member’s objectivity, and may ask a member to resign from the DSMB.

3.3 Duration of DSMB Membership and Replacement of Members

The DSMB membership will cover the duration of the Clinical Trial, including any extension of the follow-up period of the subjects.

3.4 Replacement of Members

If a member cannot continue to serve on the DSMB, the reason must be communicated in writing to the DSMB Chairperson and the Sponsor. If a member or the Chairperson leaves the DSMB, the Sponsor will select an appropriate replacement. If a member cannot reasonably be available for meetings of the DSMB, the Chairperson may request the member be replaced and the Sponsor may remove such member with the recommendation of the Chairperson. The Sponsor will be responsible for providing any new DSMB member with necessary study related materials.

4 DSMB MEETINGS

The DSMB will meet in person or by conference call according to the following schedule.

4.1 Initial Organizational Meeting

The initial meeting of the DSMB will be to acquaint the DSMB members with Protocol VIS-2014, Sponsor personnel, Sponsor communication, planned study conduct as well as other pertinent information. The DSMB may also recommend changes to this charter during this organizational meeting. Invited attendees include the DSMB members, the Medical Monitor and the Sponsor’s representatives.

4.2 Scheduled Meetings

Meetings will be held by phone or in person twice per year during the Clinical Trial. The frequency of scheduled meetings may change at the discretion of the DSMB Chairperson depending on subject enrollment and safety event rates. Meetings will also be held upon the occurrence of a device-related SAE or UADE, or at the request of the Medical Monitor.
4.3 **Quorum and Voting**

A quorum of two of the three DSMB members is required to hold any teleconference or in-person meeting. All three DSMB members must participate for a vote on any recommendation to the Sponsor other than normal continuance of the Clinical Trial.

4.4 **Meeting Format**

The meeting will begin with an open session to review enrollment, study conduct and safety information generated in the Clinical Trial. Representatives from the Sponsor and the Medical Monitor will present the information and answer any questions from the DSMB.

A closed session will follow to discuss safety data and any actions required by the DSMB regarding the available safety information. This session will be attended by only the DSMB members and, if requested with reasonable advance notice, an independent statistician retained by the Sponsor with access to the Clinical Trial database. The DSMB members will discuss the safety data, formulate any recommendations, and conduct their voting.

A final session will then convene to be attended by the DSMB members and representatives from the Sponsor and the Medical Monitor. The DSMB will verbally convey its recommendations to the Sponsor's representatives. The DSMB Chairperson will convey written DSMB recommendations within a timely fashion (within three weeks after the meeting) to the Sponsor.

5 **COMMUNICATION**

5.1 **Data Reports**

The Sponsor will prepare and provide safety data to the DSMB in advance of each meeting. All available data will be used to create a summary report and summary tables of safety data, listings of adverse events and specific case histories for selected AEs, SAEs or UADEs. The data in these tables will be drawn from active study databases. The Sponsor and Medical Monitor shall present and explain the data in the open session to the DSMB and answer any questions. The DSMB Chairperson may, on behalf of the DSMB, communicate in advance to the Sponsor a request for additional information and the Sponsor shall make reasonable efforts to comply.

If requested, the Sponsor will designate an independent statistician with access to the Clinical Trial database to be available to prepare and provide data directly to the DSMB regarding the Clinical Trial effectiveness outcomes.

The DSMB chairperson will be notified by the Sponsor or Medical Monitor upon the occurrence of a device-related SAE or UADE.

If the DSMB requests additional information concerning the study data, the DSMB Chairperson may contact the Sponsor's designated independent statisticians directly and the statistician shall be instructed by the Sponsor to provide any information reasonably requested.
5.2 **DSMB Minutes**

Following each meeting, summary minutes of both the open and closed meeting sessions will be drafted and distributed on a timely basis for approval. Minutes from open session meetings will be compiled by a Sponsor representative and reviewed by Sponsor representative(s) as well as DSMB members attending the meeting. Minutes from closed session meetings will be compiled by a DSMB member and reviewed only by DSMB members attending the meeting. Both open and closed session meeting minutes will be retained throughout the study by the DSMB Chairperson. The minutes of both open and closed meetings will be approved by the DSMB at the subsequent meeting.

Upon completion of the Clinical Trial follow-up period and the locking of the database by the CRO, the DSMB will forward a complete set of both open and the closed meeting minutes to the Sponsor.

5.3 **DSMB Recommendations**

At each DSMB meeting, the DSMB will recommend whether the study should continue, stop, or be modified based on study findings. The DSMB will provide written recommendations about the trial to the Sponsor within a timely fashion but not longer than three weeks after the meeting. In addition, the DSMB will also communicate verbally with the Sponsor's representatives immediately regarding any safety issues or other findings.

Upon receipt of the DSMB recommendations, the Sponsor will consider the recommendations, review the status of the Clinical Trial, and determine a timely course of action.

The Sponsor may identify expert individuals to review the DSMB Reports. These individuals will not have any direct involvement with the Clinical Trial but will have the clinical, statistical, and regulatory expertise needed to contribute to any decisions on behalf of the Sponsor. The Sponsor may seek input from regulatory agencies and make a decision to accept or disregard the recommendation from DSMB. The Sponsor and DSMB will assure that confidentiality of the data will be maintained.

If a DSMB recommendation is implemented, the Chairperson of the DSMB will receive written notification of this fact. If the Sponsor does not implement a recommendation, the reasons for such a decision will be documented in writing and provided to the DSMB Chairperson. The Sponsor will assume the responsibility to notify the regulatory agencies of all recommendations of the DSMB.

If the DSMB recommends stopping the trial and the Sponsor agrees, the Sponsor will inform all regulatory agencies of the decision and notify all Investigational sites. Public disclosure of the decision to stop the trial is entirely at the Sponsor's discretion.
### APPENDIX

**VIS-2014 Clinical Trial DSMB Member List**

<table>
<thead>
<tr>
<th>XXXXXXXXX, M.D.</th>
<th>INSERT ADDRESS &amp; CONTACT INFO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ophthalmologist/Optometrist</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>XXXXXXXXX, M.D.</th>
<th>INSERT ADDRESS &amp; CONTACT INFO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ophthalmologist/Optometrist</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>XXXXXXXXX,</th>
<th>INSERT ADDRESS &amp; CONTACT INFO</th>
</tr>
</thead>
</table>
APPENDIX 6: ANTERIOR SEGMENT ISCHEMIA (ASI): DETECTION, MITIGATION AND REPORTING

Anterior Segment Ischemia (ASI) is a potentially serious but most often self-limited response to decreased perfusion that even in severe cases generally resolves without sequelae or detrimental effects on vision. The rich collateral blood supply of the anterior segment likely explains its relatively benign common clinical course.

Decreased constriction of the pupil in response to light is the earliest physiological indicator of ASI and serves as a bellwether indicating diminished perfusion. Recovery of perfusion, when it occurs at this mild stage, avoids potential sequelae such as persistent pupillary abnormalities. Monitoring the pupillary reflex in the immediate postoperative period helps prevent progression by allowing prompt intervention to restore perfusion while the condition remains completely reversible.

In this clinical study of the VisAbility Implant, Refocus has adopted digital infrared dynamic pupillometry as a sensitive indicator of neuromuscular disturbance secondary to decreased iris vascular perfusion in the immediate postoperative period. Pupillometry serves the primary purpose of evaluating the impact of surgery on perfusion and allowing for prompt removal of scleral implants from eyes that demonstrate compromised perfusion, thus reversing impaired pupillary function and preventing progressive damage from ischemia.

Clinical Syndrome, Natural History and Severity Grading

ASI represents an acute, generally self-limited response of the anterior segment of the eye to decreased vascular perfusion. While mild cases most often resolve without sequelae, more severe cases may develop persistent pupillary abnormalities and iris atrophy. Though rare, cataract and hypotony have been reported in a few isolated, very severe cases.

The clinical syndrome of ASI was first described in 1954 and has become recognized as an uncommon complication of surgery involving the extraocular muscles. Risk factors for the development of ASI include advanced age, previous extraocular surgery, blood dyscrasias, hypercoagulable states, atherosclerosis, carotid artery disease and thyroid related immune orbitopathy. In the setting of strabismus surgery, these risk factors play a larger role in determining susceptibility to ASI than the number or combination of muscles operated.

Anatomical studies have demonstrated that the anterior ciliary arteries are the source of 70 to 80% of the circulation of the anterior segment, including the iris and ciliary body. The long posterior ciliary arteries provide the remainder, along with some contribution from the conjunctiva. The anterior ciliary arteries run along the rectus muscles, dividing into multiple branches and forming three levels of collateral anastomoses near the muscles’ scleral insertion points. This rich collateral circulation likely explains the rarity and generally self-limited nature of postoperative ASI.
Delayed perfusion of the iris as demonstrated by angiography is recognized as Grade 1 ASI.\(^4\) However, iris fluorescein angiography is not a useful tool in predicting which patients are likely to progress to higher grades of ASI or develop long-term sequelae postoperatively.\(^9\) Acutely decreased pupil reactivity represents Grade 2 ASI. Anterior chamber reaction in addition to decreased pupil reactivity constitutes Grade 3. Striate keratopathy, which is similar to the type of corneal edema typically seen following cataract surgery, in addition to anterior chamber reaction and decreased pupil reactivity represents the highest level of severity, Grade 4.

Patients with Grade 4 ASI typically experience pain and reduced visual acuity beginning one or two days after surgery. Without any surgical re-intervention, a period of gradual clinical improvement follows, with return of preoperative visual acuity in nine weeks or less.\(^9\) It is not known whether medical treatment with topical or systemic anti-inflammatory agents has any effect on the natural history of ASI. Patients with severe iris ischemia may develop iris atrophy, decreased pupil reactivity and an oval or irregular pupil.

Case reports and series in the literature reveal the natural history typical of ASI. For example, Forbes reported on a case of Grade 4 ASI occurring after a four muscle operation. Striate keratopathy initially reduced the visual acuity to 20/200. Over two months the vision improved to 20/30. Iris atrophy and an irregular pupil were the only sequelae.\(^5\) Keech et al described a case of Grade 4 ASI following a transposition procedure in a 74 year old woman with hypertension. On postoperative day 1, visual acuity was reduced to 20/100. Slit lamp exam revealed an oval pupil with an atonic sphincter, anterior chamber reaction and striate keratopathy. By 6 weeks all clinical signs had resolved except for a sluggishly reactive, oval pupil.\(^6\)
Saunders et al reported on a series of cases involving surgery on three extraocular muscles. They described five adult patients who developed acute ASI, including three with pupil signs and anterior chamber reaction (Grade 3) and two with striate keratopathy (Grade 4). Treatment consisted of topical and systemic steroids. With the exception of corectopia, there was complete resolution of all signs within 9 weeks postoperatively. No patient suffered permanent visual loss. Olver and Lee reported a series including 17 eyes with Grade 1, 11 eyes with Grade 2 and 5 eyes with Grade 3 ASI. Recovery of the iris circulation in most patients occurred within 4 weeks of surgery. Only 2 eyes in the entire series demonstrated long-term pupil changes; the remaining eyes had no sequelae.

To further elucidate the natural history of ASI, Bagheri et al investigated ASI in a rabbit model, chosen for its anatomic similarity to the human, including the significant contribution of the vasculature of the 4 rectus muscles to nourishment of the anterior segment. Performing various combinations of surgery involving from 1 to 4 muscles, they found that 51 eyes (30.4%) developed signs of ASI, but in most cases inflammation and corneal edema resolved spontaneously and histopathology revealed no major permanent ischemic changes. Long-term complications included pupil irregularity and decreased response to light in 12 eyes and cataract in 4 eyes. A single case in the 4-muscle group showed neovascularization of the cornea and iris. These findings support the clinically recognized natural history of ASI, which involves complete resolution without sequelae in most cases.

**Digital Pupillometry**

Because pupillary dysfunction constitutes the earliest functional sign of ASI, sensitive and precise measurement of the pupillary response to light in the immediate postoperative period represents a useful indicator of the risk of disease progression. Other methods of detecting changes in anterior segment perfusion, including iris angiography and laser Doppler flowmetry, have not been proven as useful. Iris angiography is not a useful tool for predicting which patients may develop clinical signs of decreased perfusion; therefore, iris angiography has not been standardized as a means of assessing postoperative iris perfusion, nor has it been utilized to assess the risk of sequelae. In addition, iris angiography does not reveal filling of intrastromal vessels in eyes with highly pigmented irides. Further, the dye pattern is different in each individual, with a wide range of normal filling times and patterns. Additionally, validated commercial instruments designed specifically for iris angiography are not currently available, so iris angiography requires modification of existing equipment. Lastly, iris angiography adds risk due to potential reactions to intravenous fluorescein dye and may also prove difficult due to the status of the ocular surface and subjects’ reduced ability to comply with the procedure in the immediate postoperative period due to fatigue and residual effects of intraoperative sedation.
While laser Doppler flowmetry has found utility in the study of the retinal and optic nerve head circulation, it has had only limited investigational use for the purpose of measuring the blood flow of the iris in humans.\textsuperscript{11,12,13} This technique requires adaptation of a laser delivery system, photodetector and target fixation device to a slit lamp, and while it has been used to investigate the effects of increased intraocular pressure and increased arterial pressure on perfusion, it has not to date been used to investigate the impact of reduced blood flow in the anterior ciliary arteries.\textsuperscript{14}

Therefore, digital infrared dynamic pupillometry is the optimal indicator of iris neuromuscular function relative to iris vascular perfusion. Measurement of the dynamic response of the pupil to standardized illumination is the most sensitive means to assess the eye’s recovery from surgery because pupillary abnormalities represent the earliest functional sign of anterior segment ischemia (ASI).\textsuperscript{15} The purpose of pupillometry in the immediate postoperative period in this study is to allow for timely removal of scleral implants and prevent the development of potential sequelae.

Infrared digital pupillometry consists of an integrated intense light source for pupil stimulation; an image capture system with an infrared digital camera capable of obtaining pupil measurements throughout the entire examination process (pupil diameter at rest, during light stimulation, and at the end of the stimulus), without interfering with pupil response because it provides no visible light; and a data processor to perform calculations.\textsuperscript{16} Using this type of device, i.e., the NeurOptics NPi™-200 Pupillometer (Neuroptics, Inc., Irvine, CA), the mean percent pupil constriction in a population of healthy adults has been determined to be 34\% according to the formula \( \% \text{CH} = \left( \frac{\text{dilated pupil diameter} - \text{constricted pupil diameter}}{\text{dilated pupil diameter}} \right) \times 100 \).\textsuperscript{17} The authors of this study noted that, “in only one of 2432 measurements was the percentage of reduction below 10\%.”\textsuperscript{17} Therefore, digital infrared pupillometry offers a non-invasive method of obtaining a precise, numerical clinical measurement that serves as an early indicator of risk for progressive ASI and provides a clear threshold criterion value, allowing for timely intervention. Of note, an enrollment criterion for this study excludes any subject in whom the baseline mean percent pupil constriction is less than 30\% in either eye, so that any impact of surgery on pupillary function can be readily discerned.

In this protocol we have adopted the following instrumentation, threshold criterion and standard operating procedures:

- Measurement of the pupillary reflex in both eyes with the NeurOptics NPi™-200 Pupillometer (Neuroptics, Inc., Irvine, CA)\textsuperscript{18} in the immediate post-operative period at 15-30 minute intervals and recording the pupillary reflex in the eye as a percentage constriction based on the following formula:

\[
\text{Percent Change (}\% \text{CH}) = \left( \frac{\text{dilated pupil diameter} - \text{constricted pupil diameter}}{\text{dilated pupil diameter}} \right) \times 100
\]

- A threshold criterion value of \( \% \text{CH} \geq 25\% \) constriction in the operative eye at two distinct time points at least 5 minutes apart
- Immediate removal of all PSI from any eye which does not achieve the threshold criterion within 6 hours postoperatively and before the patient is released from the facility; and
- Mandatory electronic reporting of pupil constriction values to Refocus.

This procedure is shown in the flow chart below.

These procedures are designed to allow for timely recognition of persistent reduction in the pupillary reflex and to insure removal of all implant segments from any eye at risk of developing sequelae of ASI prior to discharge of the subject from the surgical facility on the day of surgery.

**Adverse Event Reporting**

As described above, implant segments are to be removed from any eye with Grade 2 ASI (acutely decreased pupil reactivity) or Grade 3 ASI (decreased pupil reactivity plus anterior chamber reaction) persisting 6 hours postoperative; therefore, the AE category “Secondary Surgical Intervention: Implant segment removal” should be reported for these cases. At postoperative day one or later, the constellation of findings of Grade 4 ASI, i.e., corneal edema, anterior chamber
reaction and decreased pupillary reactivity, should be reported with the AE category “Grade 4 anterior segment ischemia.” Additionally, any persistent pupillary abnormalities due to reduced iris vascular perfusion should be reported with the AE category, “Pupil abnormalities persisting after 3 months.”


APPENDIX 7: SPONSOR COMMITMENTS

Refocus Group, Inc. is committed to:

1. Complying with the Declaration of Helsinki, and all applicable health authority regulations governing the conduct of clinical research studies.

2. Protecting the rights, health, safety and welfare of study subjects.

3. Informing the clinical investigators of any new information about the study which may affect the health, safety or welfare of the subjects, or may influence their decision to continue participation in the study.

4. Providing the clinical investigators with the study protocol, and a full set of Case Report Forms on which to document the study evaluation variables for each subject entered into the study.

5. Providing the statistical analysis and study report writing resources necessary to complete reporting of the study results.

6. Ensuring equity of consideration among all investigators in multicenter studies in all matters of publications, meeting presentations, etc.

7. Certifying that IRB approval of the protocol and Investigator’s Clinical Agreement will be completed prior to initiation of study at an investigational site.
APPENDIX 8: INVESTIGATOR COMMITMENTS AND RESPONSIBILITIES

Each Investigator must be a licensed physician who has completed a residency in ophthalmology. The investigators have the following responsibilities:

1. Subject Selection

The investigator is responsible for assuring that all subjects enrolled and determined eligible for the study meet all inclusion and exclusion criteria stated in this protocol.

2. Informed Consent

The investigator is responsible for fully reviewing the nature of the study, the possible risks, and alternative treatments with prospective subjects prior to their enrollment in the study. The investigator is responsible for obtaining written Study Informed Consent in compliance with 21 CFR 50 for each subject, prior to performing surgery on a subject. The original signed Informed Consent Form will be maintained in the subject’s medical record, and a redacted copy of the signed Informed Consent Form will become an integral part of each Case Report file provided to the Sponsor.

3. Institutional Review Board (IRB) Approval

The investigator will obtain or verify approval for his/her participation in this study from the IRB for the institution at which the procedure will be performed, prior to enrolling any subjects in the study. The Informed Consent document to be used must also be approved by the IRB prior to initiation of the study.

4. Subject Evaluations and Data Reporting

The investigator is responsible for performing the subject evaluations as described in the study protocol. All information generated by the subject evaluation will be recorded on the subject source document or case report forms. The investigator will sign and date each individual form upon its completion. Originals of all case report forms will be retained in the investigator’s office in order to be available for monitoring by authorized regulatory bodies.

The investigator will not deviate from the study protocol without prior approval from the Sponsor unless protection of the health, safety or welfare of study subjects requires prompt action.

5. Record Retention

The investigator shall maintain all subject records for whichever of the following periods is shortest:

- A period of two years after the date on which the FDA approves the marketing of the device for the purpose that was the subject of the study.
- A period of five years after the date on which the results of the study are submitted to the FDA in support of the marketing of the device for the purpose that was the subject of the study.
6. **Investigational Material Accountability**

The investigator must maintain accurate records of the receipt, use and return of all investigational devices, including the product identification and serial numbers as applicable. The investigator must assure that study supplies be dispensed only to subjects enrolled and eligible to be in the study and under the direct supervision of the investigator or co-investigators.

The principal investigator must keep records of all investigational supplies. Investigational material accounting procedures must be completed before the study is considered completed.
APPENDIX 9: DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
- 29th WMA General Assembly, Tokyo, Japan, October 1975
- 35th WMA General Assembly, Venice, Italy, October 1983  41st
- WMA General Assembly, Hong Kong, September 1989
- 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
- 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
- 53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
- 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
- 59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject’s freely-given informed consent, preferably
in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject’s dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.
C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
   - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
   - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient’s decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.